AACR CANCER PROGRESS REPORT 2021

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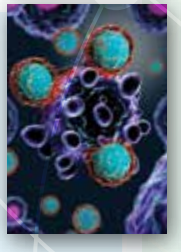










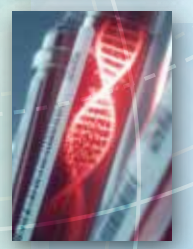

DISCOVERY SCIENCE
DRIVING CLINICAL BREAKTHROUGHS

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American Association for Cancer Research®

FINDING CURES TOGETHER®

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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 49,000 laboratory, translational, and clinical researchers; population scientists; other health care professionals; and patient advocates residing in 128 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, with more than 74,000 attendees for the 2020 virtual meetings and more than 22,500 attendees for past in-person meetings. In addition, the AACR publishes nine 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 **www.AACR.org**.

A MESSAGE FROM THE AACR

This is a time of extraordinary promise in cancer science and medicine. In the United States, overall cancer incidence and death rates are declining steadily, and an increasing number of individuals are surviving longer after a cancer diagnosis. Transformative research and technological innovation enabled by five decades of federal investments, which were catalyzed by the National Cancer Act, have led to unprecedented progress against formerly intractable cancers such as metastatic melanoma and lung cancer. Since the onset and spread of Coronavirus Disease 2019 (COVID-19) in early 2020 the pandemic has negatively impacted every aspect of cancer research and patient care. Encouragingly, cancer researchers were uniquely positioned to respond to COVID-19 and have played a vital role in combating the public health crisis of COVID-19 while continuing their quest to prevent and cure cancer.

The *AACR Cancer Progress Report 2021* provides a comprehensive overview of the remarkable progress being made because of medical research supported primarily by federal investments in the National Institutes of Health (NIH) and in particular the National Cancer Institute (NCI). As emphasized in this report, federal funding for medical research has deepened our knowledge of the complexities of cancer and accelerated the rate at which this knowledge is being harnessed to develop new and better approaches to preventing, detecting, diagnosing, treating, and curing cancer.

Among the 16 new treatments that were approved by the U.S. Food and Drug Administration (FDA) in the 12 months covered in this report are 11 molecularly targeted therapeutics that are an integral part of the precision medicine revolution in cancer care. The surge in the number of molecularly targeted therapeutics is being fueled by discoveries in cancer genomics wrought by multidisciplinary teams of researchers. The first ever approval of a molecularly targeted therapeutic against *KRAS*, one of the most frequently altered genes linked to cancer and long assumed to be "undruggable," underscores the remarkable progress in our understanding of cancer biology and a watershed moment in cancer drug discovery.

Another area of cancer treatment in which extraordinary progress is being made is immunotherapy. The use of immune checkpoint inhibitors—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 the FDA for treating just one type of cancer. As of July 31, 2021, there are eight checkpoint inhibitors approved by the FDA, and one or more of these therapeutics have been approved for the treatment of 18 types of cancer and any type of solid tumor characterized by certain molecular characteristics. A breakthrough in cancer immunotherapy discussed in this report is the first approval of a CAR T-cell therapy for patients with multiple myeloma. By expanding our knowledge of the immune system and its interactions with cancer cells and by facilitating the convergence of experts from an increasingly diverse array of disciplines, more clinical breakthroughs in immunotherapy will be achieved for the benefit of patients worldwide.

Despite these significant strides, we must continue our quest for newer and more innovative methods to detect and eradicate cancer while keeping our patients healthy. This urgent need is underscored by the sobering reality that cancer will claim more than 608,000 lives in the United States this year. This number is predicted to increase considerably in the coming decades because cancer is largely a disease of aging, and the segment of the U.S. population age 65 and older is growing. Therefore, it is critical to actively develop and successfully implement newer and more effective strategies for cancer prevention, early detection, diagnosis, and treatment.

Moving forward, we must ensure that everyone benefits from groundbreaking advances against cancer. Cancer can strike anyone—regardless of age, gender, race, ethnicity, socioeconomic status, location, or political affiliation. No one is immune to this devastating disease. 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. Participation of minorities and other underserved populations in clinical trials that are testing lifesaving new anticancer therapeutics continues to be disappointingly low. We must adopt new approaches to encourage and enroll an ever-increasing number of cancer patients in clinical trials so that research can identify the most efficacious approaches to help all patients. Minorities and the underserved have also been disproportionately impacted by COVID-19 as well as by the pandemic-related disruptions to health care, including cancer care. It is imperative that all stakeholders in the medical research community work together to eliminate the health care disparities related to both cancer and COVID-19.

We are at an inflection point in cancer research. Major milestones in discovery science over the past five decades have created opportunities for the next wave of breakthroughs that were not previously possible. We now have the scientific knowledge, cutting-edge technologies, and capability to deliver unprecedented advances to cancer patients. Also, there is bipartisan leadership in Congress that has delivered steady, significant annual funding increases for the NIH and in particular the NCI. As we recover from the impact of COVID-19, 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. The AACR urges Congress to continue to support robust, sustained, and predictable annual growth of the NIH budget, and to provide consistent and sufficient annual funding for the U.S. Food and Drug Administration (FDA) and the Centers for Disease Control and Prevention (CDC). These actions will ensure that major strides are made toward the goal of preventing and curing all cancers at the earliest possible time.

David A. Tuveson, MD, PhD, FAACR
AACR President

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

EXECUTIVE SUMMARY

Transformative research and technological innovation are driving unprecedented progress against the collection of diseases we call cancer. Despite the significant barriers created by the Coronavirus Disease 2019 (COVID-19) pandemic to many aspects of medical research and cancer patient care, scientists have continued their quest to cure cancer, while responding to the challenges posed by the pandemic through innovative adaptations across the continuum of cancer science and medicine.

"I look forward to a world where people can live beyond their cancer. Indeed, our prospects for making substantial advances for cancer patients through research have never been higher than today."

David A. Tuveson, MD, PhD, FAACR;
AACR President, 2021-2022

As the first and largest professional organization in the world with a steadfast mission to prevent and cure all cancers, American Association for Cancer Research (AACR) is dedicated to increasing public understanding of cancer and the important role of medical research in saving lives. AACR is also committed to advocating for increased annual federal funding to government entities that drive progress against cancer and improve public health, in particular, National Institutes of Health (NIH), National Cancer Institute (NCI), U.S. Food and Drug Administration (FDA), and Centers for Disease Control and Prevention (CDC).

The annual AACR Cancer Progress Report to Congress and the American public is a cornerstone of the AACR's educational and advocacy efforts. This eleventh edition of the report highlights how research continues to transform lives, like the lives of the courageous individuals featured in the report who have shared their experiences with cancer. It also underscores how the COVID-19 pandemic has negatively affected cancer research and care, as well as how unwavering bipartisan support from Congress, in the form of robust and sustained annual increases in funding for NIH, NCI, and FDA, is vital if we are to accelerate the pace of progress against cancer for the benefit of individuals everywhere.

Cancer in 2021

Research is the backbone of progress against cancer because it spurs the development of novel and better approaches to preventing, detecting, diagnosing, treating, and curing many of the diseases we call cancer. These advances are driving down overall U.S. cancer incidence and death rates and increasing the number of individuals who are surviving longer after a cancer diagnosis. For example, the age-adjusted overall U.S. cancer death rate declined by 31 percent from 1991 to 2018, which is the last year for which these data are available. Rapid declines in the death rates from aggressive tumors, such as lung cancer and melanoma, over the last decade have contributed significantly to this reduction in overall cancer deaths. In addition, the U.S. 5-year relative survival rate for all cancers combined has increased from 49 percent for people diagnosed in the mid-1970s to 68 percent for those diagnosed from 2011 to 2017.

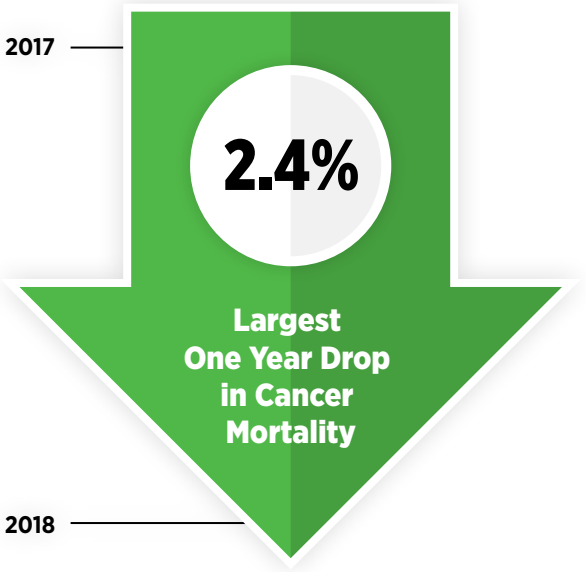
Even though we are making significant progress, cancer continues to be an enormous public health challenge in the United States and around the world. One challenge is that the number of new cancer cases is projected to increase dramatically in the coming decades, rising from nearly 1.9 million in 2021 to more than 2.2 million in 2040 in the United States alone. This sharp increase is anticipated largely because of the overall population growth and because the segment of the U.S. population that accounts for most cancer diagnoses—those age 65 and older—is expanding.

Another pressing public health challenge is that the burden of cancer is shouldered disproportionately by racial and ethnic minorities and other underserved populations. Racial and ethnic minorities have also shouldered a disparate burden of the ongoing COVID-19 pandemic, laying bare stark inequities in health care. It is imperative that all stakeholders play a role in eradicating the systemic and structural injustices that are barriers to health equity.

The immense toll of cancer is felt not only through the number of lives it affects each year, but also through its significant economic impact. In the United States, an estimated $200.7 billion of total health care costs was spent on cancer-related health care in 2020. That number is projected to increase to $245.6 billion by 2030. These costs do not reflect the additional indirect economic burden due to lost earnings or lost productivity or the potential adverse impacts of COVID-19 on cancer-related health care. With the personal and economic burden of cancer predicted to rise in the next few decades, it is vital that the nation invests in the groundbreaking research that drives progress against cancer.

Understanding How Cancer Develops

Discoveries across the spectrum of cancer research from basic science to translational, clinical, and population research have led to our current understanding of how cancer arises and develops. We now understand that cancer is a collection of diseases that arise when the processes that control normal



cell growth, cell division, and cellular life span go awry. This happens primarily because of changes, or mutations, in the genetic material of normal cells. The identity of genetic mutations and the order and speed at which a cell acquires them determine the length of time it takes a given 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 radiation (UV) 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 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

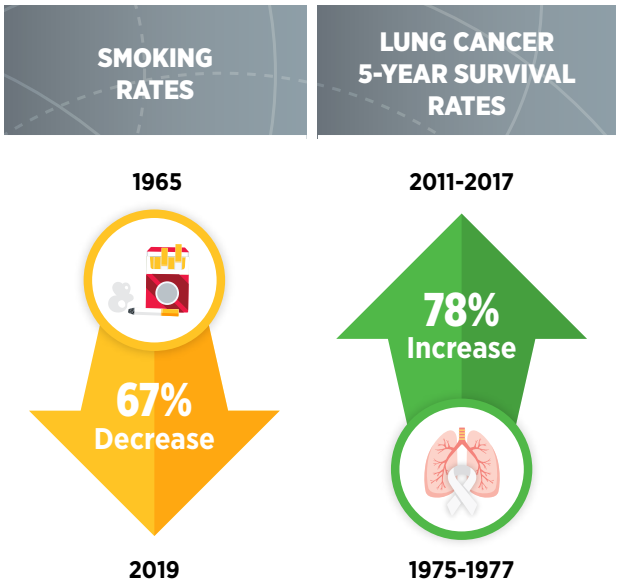
Decades of research have led to the identification of numerous factors that increase a person's risk of developing cancer. Given that exposure to many of these factors can be eliminated or reduced, many cases of cancer can be prevented. In fact, it is estimated that about 40 percent of cancer cases in 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 declined steadily from 42 percent in 1965 to 14 percent in 2019. However, the current popularity of electronic cigarettes (e-cigarettes) among U.S. youth and young adults threatens to reverse our significant progress against tobacco use. Recent legislations that raise the federal minimum age of sale of all tobacco products, including e-cigarettes, to 21 years, and impose restrictions on kid-friendly e-cigarette flavors have the potential to accelerate future progress against tobacco-related diseases.

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 trends threaten to slow the rapid decline in overall cancer death rates that we have experienced in recent years.

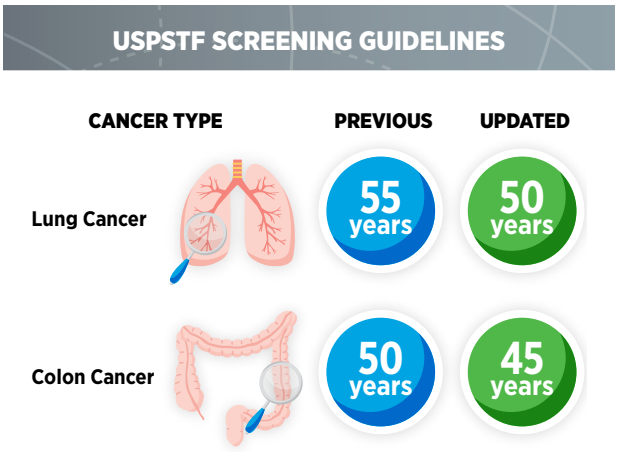
Therefore, it is essential that all stakeholders work together to enhance the dissemination of our current knowledge of cancer



risk prevention and implement evidence-based policies to minimize the incidence, morbidity, and mortality of cancers attributable to preventable causes.

Screening for Early Detection

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 checked. Research discoveries that have deepened our understanding of cancer initiation and progression are the foundation of screening strategies to detect precancerous lesions or cancer at an early stage of development. Finding precancerous lesions or cancer at an early



stage of development makes it more likely that a cancer can be intercepted and a patient can be treated successfully.

Determining whether broad implementation of a cancer screening test across a defined population can decrease deaths from the screened cancer and provide benefits that outweigh the potential risks of undergoing the test requires extensive research and careful analysis of the data generated. Currently, there are five types of cancer—breast, cervical, colorectal, lung, and prostate cancer—for which screening tests have been used to monitor large segments of the U.S. population. During the 12 months covered in this report, U.S. Preventive Services Task Force (USPSTF), an independent volunteer panel of experts in prevention and evidence-based medicine, updated their guidelines for colorectal and lung cancer screening by expanding the age-based eligibility to a broader population.

Every person has a unique risk for each type of cancer based on genetic, molecular, and cellular makeup, lifetime exposures to cancer risk factors, and general health, as well as the person's own tolerance of the potential risks of a screening test. Therefore, individuals should consult with their health care practitioners to develop a personalized cancer prevention and early detection plan.

Discovery Science Driving Clinical Breakthroughs

The dedicated efforts of individuals working throughout the continuum of cancer science and medicine are constantly powering the translation of new research discoveries into lifesaving advances for people in the United States and around the world. Between August 1, 2020 and July 31, 2021—the 12-month period covered in this report—FDA approved 16 new anticancer therapeutics and expanded the use of 11 previously approved anticancer therapeutics for treating new cancer types.

Several of these approvals are groundbreaking advances.

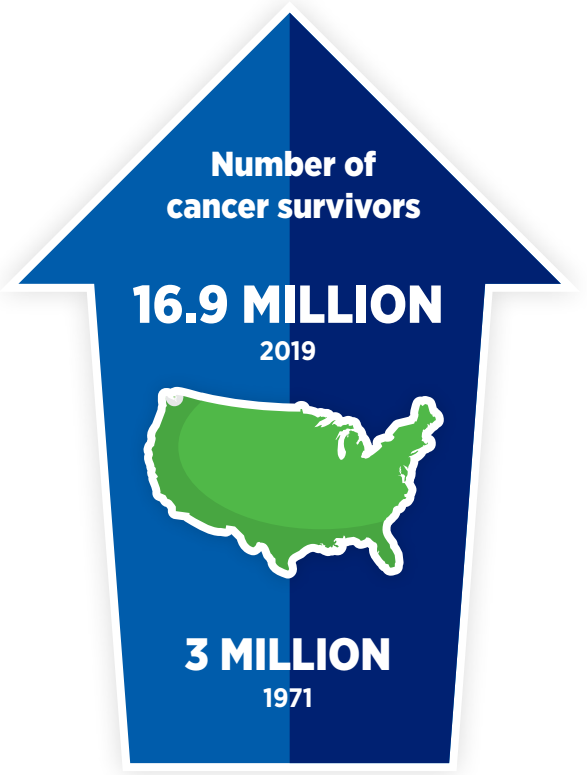
In May 2021, FDA approved the first molecularly targeted therapeutic against the protein KRAS, which has long been considered an undruggable target, for the treatment of certain patients with lung cancer. The therapeutic, sotorasib (Lumakras), targets an altered form of the protein, known as KRAS G12C, and is providing a new treatment option and new hope for patients with non–small cell lung cancer such as **Steve Castellaw** (see p. 94).

In March 2021, FDA approved the first CAR T-cell therapy for the treatment of patients with multiple myeloma such as **David Wellenstein, MD** (see p. 118). In April 2021, FDA approved a new immune checkpoint inhibitor, dostarlimab-gxly (Jemperli), for treatment of patients with endometrial cancer such as **Patricia Hawkins** (see p. 110) whose tumors have a specific genetic feature. Both CAR T cells and immune checkpoint inhibitors are types of immunotherapeutics, a class of revolutionary anticancer agents that have been shown to yield remarkable responses for many patients with advanced cancers.

Supporting Cancer Patients and Survivors

Research-fueled advances in cancer detection, diagnosis, and treatment are helping more and more people to survive longer and lead fuller lives after a cancer diagnosis. According to the latest estimates, more than 16.9 million U.S. adults and children with a history of cancer were alive on Jan. 1, 2019, compared to just 3 million in 1971.

Rapid advances across the continuum of cancer research and care have also highlighted the current gaps in our knowledge that require additional research. We have learned that survivors of cancer still face serious and persistent adverse outcomes, including physical, emotional, and psychosocial challenges,



because of their disease and treatment. Each person diagnosed with cancer faces his or her own unique set of challenges. For example, an estimated 25 percent of cancer survivors report poor physical health and 10 percent report poor mental health, both adversely affecting quality of life. Researchers are exploring ways to utilize healthy behaviors, palliative care, psycho-oncology, and other evidence-based strategies to improve survival and quality of life for patients with cancer and survivors of cancer. For example, research has shown that an active lifestyle is especially beneficial to cancer survivors because it can help mitigate the numerous physical, mental, and emotional challenges they 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 different age groups.

Looking to the Future

Research drives progress against cancer because it provides us with a deeper understanding of cancer biology.

As we look to the future, many researchers, including **AACR President, 2020–2021, David A. Tuveson, MD, PhD, FAACR**, (see p. 136), 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 deeper insight into the mechanisms underlying cancer development and identify novel ways to target and eradicate cancer cells. In addition, incorporation of cutting-edge technologies, such as liquid biopsies and artificial intelligence (AI), will allow us to achieve the full potential of precision medicine by addressing a wide range of unsolved clinical questions across the spectrum of cancer research and care.

Combating Cancer Through Science-based, Patient-centered Policies

Federal investments in NIH, NCI, FDA, and CDC have fueled tremendous advances against cancer by catalyzing scientific discoveries and facilitating the translation of these discoveries into new and better anticancer medical products and community-based programs to save lives and improve public health.

To continue to make strides against cancer, we need robust, sustained, and predictable annual budget increases for NIH and NCI. We also need ongoing congressional commitment to support the important role of FDA to ensure the safety and efficacy of anticancer therapeutics, and to support the cancer prevention and control programs at CDC. These vital investments will help diversify the research workforce, advance regulatory science initiatives, and allow us to pursue policies that improve cancer prevention, early detection, and control for individuals, families, and communities.

The AACR Call to Action

The extraordinary advances against cancer detailed in this report were made possible by the dedicated 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, making it possible to prevent, detect, diagnose, treat, and cure many types of cancer that previously lacked effective treatment options. These advances are driving down overall U.S. cancer incidence and death rates and increasing the number of individuals who are surviving longer after a cancer diagnosis.

Thanks to the remarkable bipartisan efforts of Congress, NIH funding has increased by nearly $13 billion or 42 percent from FY 2015 to FY 2021. These significant investments make it possible for researchers across the country to continue making advances against cancer and many other diseases.

Despite this progress, much more work needs to be done on behalf of those living with cancer and those who will be diagnosed in the future. For example, there are still no effective treatments for many of the over 200 known types of cancer. Furthermore, the COVID-19 pandemic has had a profoundly negative impact on medical research and cancer care, bringing many critical projects to a halt, delaying screening and treatments, and diverting resources to the immediate need of responding to COVID-19. The adverse consequences of the COVID-19 pandemic will be felt for years and perhaps decades to come.

As the United States recovers from the devastating toll of the COVID-19 pandemic, we are reminded of the enormous value of medical research in overall public health. Decades of investment in basic, translational, and clinical research have enabled scientists to develop diagnostics, treatments, and vaccines for this novel disease at a pace never seen before. This robust approach to medical research has already saved hundreds of thousands of lives from COVID-19 in the United States alone. Cancer researchers were uniquely positioned to respond to the challenges posed by COVID-19 and have played a vital role in combating the pandemic while continuing their quest to cure cancer. With so many promising opportunities ahead of us it is critical that we maintain our momentum of progress against cancer.

AACR deeply appreciates the commitment of Congress to expediting progress against cancer and other diseases through robust funding increases for NIH, as well as to supporting the critical regulatory science work at FDA and public health programs of CDC.

THEREFORE, AACR URGES CONGRESS TO:

- Continue to support robust, sustained, and predictable growth for NIH and NCI by providing increases in their FY 2022 base budgets of at least $3.2 billion and $1.1 billion, respectively, for a total funding level of $46.4 billion for NIH and $7.6 billion for NCI.

- Ensure that the funding designated through the 21st Century Cures Act for targeted initiatives, including the National Cancer Moonshot, is fully appropriated in FY 2022 and is supplemental to the overall increase in the NIH base budget.
- Provide at least $10 billion for NIH in emergency supplemental funding to restart research and clinical trials that have been put on hold due to the pandemic, as proposed in the Research Investment to Spark the Economy (RISE) Act of 2021.
- Provide $50 million for the third year of the Childhood Cancer Data Initiative and no less than $30 million for the continued implementation of the Childhood Cancer STAR Act.
- Support 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.
- Support FDA's critical regulatory science initiatives and advance the development and regulation of oncology products by providing an increase of at least $343 million in discretionary budget authority in FY 2022, as recommended in President Biden's budget proposal.
- Support vital CDC Cancer Prevention and Control Programs with total funding of at least $559 million. This includes funding for comprehensive cancer control, cancer registries, and screening and awareness programs for specific cancers.

If we hope to reach the day when cancer is no longer a major health threat to our nation's citizens, Congress must provide robust, sustained, and predictable annual funding increases for NIH, NCI, FDA, and CDC in FY 2022 and beyond. These investments will help us transform cancer care, increase survivorship, spur economic growth, and maintain the position of the United States as a global leader in scientific and medical research and specifically in cancer research. Most importantly this will continue to bring lifesaving cures to the millions of people worldwide whose lives are touched by cancer.

A SNAPSHOT OF

A YEAR IN PROGRESS

1991 —

31%

Reduction in overall cancer death rate

>3.2 MILLION LIVES SAVED

2018 ——————

BETWEEN AUGUST 1, 2020 AND JULY 31, 2021, THE FDA APPROVED:

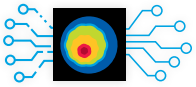
16 new anticancer therapeutics, which are now benefiting patients with various types of cancer

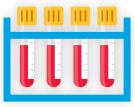
11 previously approved anticancer therapeutics for treating new types of cancer

3 new diagnostic imaging agents

2 new surgery guiding devices

1 new artificial intelligence-driven endoscopy device





2 new multipanel NGS liquid biopsy companion diagnostic tests

RESEARCH CONTINUES TO ADVANCE IMMUNOTHERAPY, LEADING TO:

The first approval of a CAR T-cell therapy for the treatment of patients with multiple myeloma, such as **David Wellenstein, MD** (see p. 118)

A new immune checkpoint inhibitor to treat patients with endometrial cancer who have certain biomarkers in the tumor, such as **Patricia Hawkins** (see p. 110)

The first approval of immune checkpoint inhibitors for treating patients with mesothelioma, such as **Susan Falbo** (see p. 112)

RESEARCH CONTINUES TO POWER PRECISION MEDICINE, LEADING TO:

The first therapeutic to target KRAS, which is providing new hope to patients with non–small cell lung cancer, such as **Steve Castellaw** (see p. 94)

The first antibody-drug conjugate for treating patients with HER2-positive gastric cancer, such as **Bryan Chagolla** (see p. 100)

The first oral hormone therapy for treating patients with advanced prostate cancer (p. 105)

50TH ANNIVERSARY OF THE

NATIONAL CANCER ACT OF 1971

President Nixon signed the National Cancer Act at a ceremony in the East Room on December 23, 1971.

"I hope in the years ahead we will look back on this action today as the most significant action taken during my Administration."

Richard M. Nixon

The year 2021 marks the 50th anniversary of the National Cancer Act of 1971, a groundbreaking legislation that launched a national commitment to making progress against cancer by providing the National Cancer Institute (NCI) with broad authorities and innovative mechanisms to drive our understanding of this devastating collection of diseases. Years of advocacy by patients and survivors of cancer, researchers, physicians, and others led to the introduction and eventual passage of the bill, which was signed into law by President Richard Nixon on December 23, 1971.

The National Cancer Act significantly expanded the authority of the NCI director, making the position a presidential appointment and authorizing the director to submit a professional judgment or "bypass" budget directly to the president. This annual budget outlines opportunities in cancer research and the funds needed to fulfill them. The legislation also mandated the establishment of the National Cancer Advisory Board, a panel of experts that advises and assists NCI in carrying out its programs, as well as the creation of the President's Cancer Panel, a three-member group that submits an annual report to the President on selected topics in cancer research.

One of the most consequential provisions of the National Cancer Act was the establishment of the NCI Cancer Centers Program to recognize and support institutions across the country that are leading the way in cancer treatment, diagnosis, and prevention. The legislation initially provided the funding to establish 15 cancer research centers and local cancer control programs. Today, there are 71 NCI-designated cancer centers across 36 states and the District of Columbia (see **Figure 1**, p. 9).

In the fifty years since the Act was signed into law, NCI-designated cancer centers have been at the forefront of new discoveries in basic, clinical, and translational science that have revolutionized the way we understand and treat cancer. These centers also serve as the point of care for patients in their communities and beyond, providing access to the best treatments currently available as well as cutting-edge new therapies through clinical trials. Many of these institutions also provide community-based cancer screening services and public education in collaboration with local partners. Additionally, NCI-designated cancer centers lead the way in training the next generation of cancer scientists through a variety of educational programs, fellowships, and mentorship opportunities.

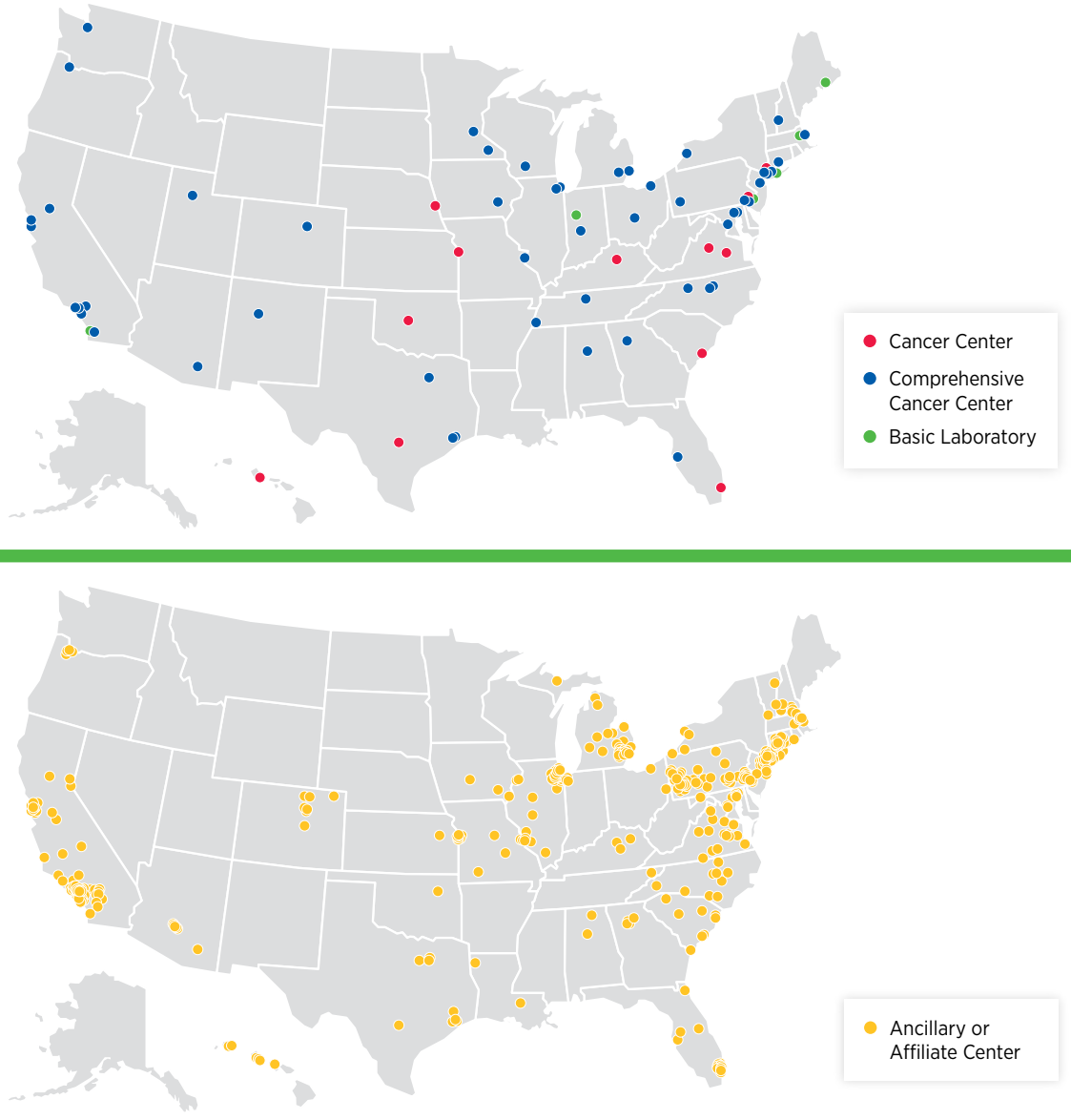
"The National Cancer Act of 1971 was a watershed moment in our nation's fight against this terrible family of diseases. Advocates and survivors worked passionately with Congress to develop historic legislation to establish a nationally coordinated approach to cancer research that led to 50 years of dramatic advances in preventing, treating, and even curing cancer. Commemorating this anniversary is a reaffirmation of the original intention of the National Cancer Act—a time to once again unite as one community to declare that Nothing Will Stop Us from ending cancer as we know it."

Norman E. Sharpless, MD; NCI Director

FIGURE 1

NATIONAL CANCER ACT
50 YEARS
1971-2021

NCI-DESIGNATED CANCER CENTERS



The NCI Cancer Centers Program was created under the National Cancer Act of 1971 and has become a cornerstone of our nation's cancer research and clinical care infrastructure. There are currently 71 NCI-Designated Cancer Centers, located across 36 states and the District of Columbia. These institutions are classified in three categories: Cancer Centers, which are recognized for their scientific leadership and resources in multiple facets of cancer research; Comprehensive Cancer Centers, which demonstrate additional depth or breadth of research, including transdisciplinary cancer research; and Basic Laboratories, which focus primarily on laboratory research and preclinical translation. Many of the NCI-Designated Cancer Centers have ancillary or affiliate sites offering additional services to the communities in which they are located.

For more information, visit https://www.cancer.gov/research/infrastructure/cancer-centers.

CANCER IN 2021

In this section, you will learn:

- In the United States, the overall age-adjusted cancer death rates have decreased by 31 percent from 1991 to 2018, a reduction that translates into 3.2 million cancer deaths avoided.
- The decline in the overall cancer death rate is driven in large part by dramatic reductions in lung cancer and melanoma death rates.
- Progress has been made in understanding, and in some cases reducing, cancer health disparities since the 1990s. However, cancer still disproportionately affects racial and ethnic minorities and other underserved populations.
- Identifying the underlying causes of the rising incidence in certain early-onset cancers is critical for continued progress against cancer.
- While the Coronavirus Disease 2019 (COVID-19) has adversely affected all aspects of cancer research and care, scientists have responded in new and innovative ways to address the unique challenges posed by the pandemic.
- Robust and sustained cancer research funding is a vital investment for the U.S. economy.

Research: Driving Progress Against Cancer

Advances in basic, clinical, translational, and population sciences are the catalysts that drive progress against cancer through improvements in prevention, detection, diagnosis, treatment, and survivorship. Research is also the driving force behind every new policy designed to improve public health. The collective impact of cancer research is felt through the numerous lives saved every year in the United States (U.S.) and, increasingly, across the globe (1). Advances at each level of cancer care stem from years-long interdisciplinary collaborations among stakeholders across the medical research community (see sidebar on **Driving Progress Against Cancer Together**, p. 11).

The year 2021 marks the 50th anniversary of the National Cancer Act that was signed into law by President Richard M. Nixon (2). The National Cancer Act placed a vital focus on the etiology, diagnosis, prevention, and treatment of cancers and, through multiple administrative and budgetary initiatives, enabled a cross-disciplinary approach to accelerate the pace of progress against cancer (see **50th Anniversary of the National Cancer Act 1971**, p. 8) (2). Over the past five decades, the United States has made substantial progress in the fight against cancer, as underscored by the steadily declining overall cancer mortality rates. As a result, increasing numbers of children (ages 0-15), adolescents and young adults (AYA) (ages 15-39), and older adults (40 years and older) are surviving after a cancer diagnosis (3). The 5-year relative survival rate for all cancers combined has increased to 68 percent for people diagnosed between 2011 and 2017 from 49 percent for those diagnosed in the mid-1970s (4). This encouraging trend is also evident among U.S. children and adolescents (ages 0 to 19), for whom the 5-year relative survival rose from 63 percent to 84 percent over the same time interval (3) (see **Figure 2**, p. 12).

The extraordinary progress against cancer in the United States is further highlighted by a 31 percent decline in the age-adjusted overall cancer death rate from 1991 to 2018, which is the most recent year for which data are available. This includes a record 2.4 percent decline in the age-adjusted overall U.S.

THE HONORABLE

Rosa DeLauro

U.S. Representative for Connecticut's 3rd District

Chair, House Appropriations Committee and Subcommittee on Labor, Health and Human Services, Education, and Related Agencies

"A breakthrough at the National Institutes of Health, specifically the National Cancer Institute, saves not just one life but potentially millions of lives over generations. As an ovarian cancer survivor and chair of the committee that funds these programs, I know firsthand the importance of investing in cancer research. I am proud to have led my colleagues in nearly tripling funding for NIH since I was first elected, and these increases have funded critical work on prevention, detection, diagnostics, and treatments. With U.S. cancer death rates steadily declining, we must continue to work together to increase these critical investments."

DRIVING PROGRESS AGAINST CANCER TOGETHER

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

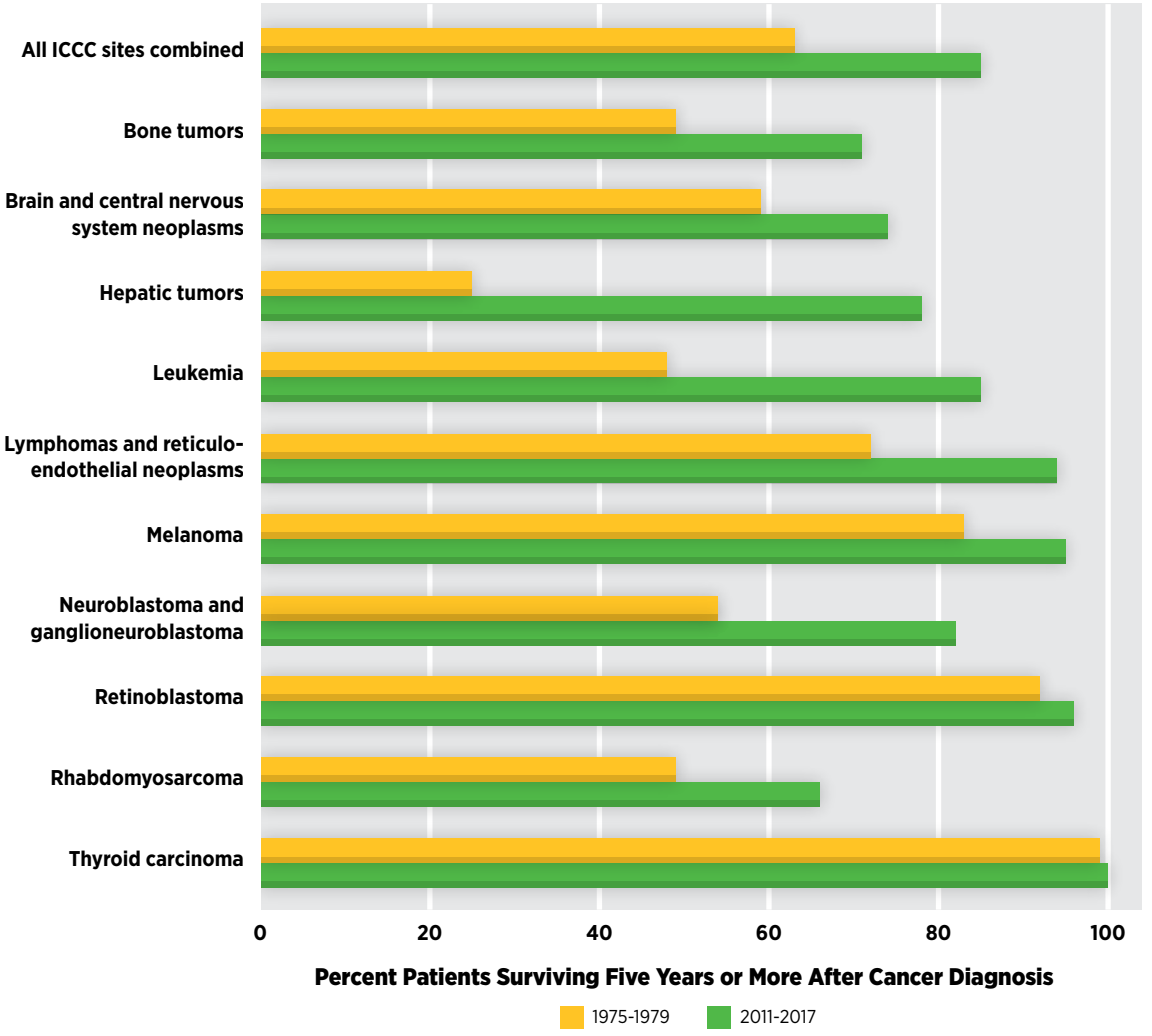
cancer death rate between 2017 and 2018, the largest reduction ever seen in a single year, and the second consecutive year in which a record decline in a single year was documented (3). The reduction in cancer death rates between 1991 and 2018 translates into 3.2 million cancer deaths avoided (4).

The steady decline in overall cancer-related deaths in the United States in the past five decades can be attributed largely to the bench-to-bedside advances across the continuum of cancer science and medicine (see **Supplemental Figure 1**, p. 192). Transformative discoveries, catalyzed by federal funding for cancer research, are rapidly culminating in improved prevention, early detection, diagnosis, and treatments for cancer. In this report, we highlight the advances made during the 12 months from August 1, 2020 to July 31, 2021. During this period, FDA approved 16 new anticancer treatments, three new cancer

FIGURE 2

NATIONAL CANCER ACT
50 YEARS
1971-2021

FIVE DECADES OF PROGRESS AGAINST CHILDHOOD AND ADOLESCENT CANCERS



Five-year relative survival rates for the U.S. children and adolescents (ages 0–19) who were diagnosed with cancer from 2011 to 2017 were substantially increased compared to those diagnosed from 1975 to 1979. Childhood cancers are classified using the International Classification of Childhood Cancers (ICCC) (5). The improvement in 5-year relative survival rate was seen for all ICCC sites combined, for groups of cancers considered together, and for individual types of cancer.

Data from (4,6).

imaging agents, and two new cancer surgery guiding devices. Over these 12 months FDA also expanded the use of 11 previously approved anticancer therapeutics to treat additional cancer types (see **Progress Across the Spectrum of Cancer Treatment**, p. 76). As we continue to make scientific and policy strides in cancer prevention, etiology, detection, diagnosis, treatment, and survivorship, we will seize the moment and maintain the momentum of progress against cancer.

THE HONORABLE

Tom Cole

U.S. Representative for Oklahoma's 4th District

Ranking Member, House Appropriations Subcommittee on Labor, Health and Human Services, Education, and Related Agencies

"For 50 years, the National Cancer Act has been critical in the battle against cancer by making investments in cancer research. I am proud to be Ranking Member on the House Appropriations subcommittee responsible for funding increases in cancer research through the National Institutes of Health and the National Cancer Institute. Because of these joint efforts, significant advancements have been made in cancer prevention, detection, diagnosis and treatment that have led to saving thousands of lives."

HARNESSING CROSS-DISCIPLINARY COLLABORATIONS TO IMPROVE OUTCOMES FOR PATIENTS WITH METASTATIC CANCERS

The steady decrease in overall cancer-related deaths in the United States since the signing of the National Cancer Act in 1971 is driven primarily by progress against the five most common cancer types: breast cancer, prostate cancer, lung cancer, colorectal cancer, and melanoma (3). Of these cancer types, progress made against various subtypes of lung cancer, including those that have spread to other parts of the body (metastatic), offers instructive insights into the collective and positive impact of cross-disciplinary approaches to basic, translational, and clinical research, population sciences, and public policy in combating this devastating disease.

Public Education and Policy Driving Progress in Lung Cancer Prevention

Tobacco use is the leading cause of preventable diseases, which includes 17 types of cancer in addition to lung cancer (7–9). In the United States, implementation of concerted nationwide public education campaigns, as well as comprehensive tobacco control policies at federal, state, and local levels, has played a central role in reducing smoking rates. The landmark 1964 Surgeon General's report, *Smoking and Health*, was the first comprehensive look at the accumulating scientific evidence—the report reviewed more than 7,000 research articles—linking tobacco use to lung cancer and other diseases (10). Since then, 33 additional reports have been issued by U.S. Surgeon Generals; these reports have highlighted hazards of tobacco use and have served as a guiding principle to draw and introduce legislation for tobacco control (11).

In the past five decades, major tobacco control policies have become laws at all levels of government (see **Figure 3**, p. 14). These laws have changed social norms surrounding smoking (13); decreased the use of tobacco (14,15); increased the financial cost of producing, distributing, and buying tobacco products (16); and raised the federal minimum age of sale of all tobacco products from 18 to 21 (also see **Reducing Tobacco-related Illness Through Public Health Policy**, p. 148) (15). In parallel, multiple U.S. government agencies, including Centers for Disease Control and Prevention (CDC), Food and Drug Administration (FDA), National Cancer Institute (NCI), and National Institutes of Health (NIH), have deployed concerted and coordinated tobacco control strategies. These efforts are exemplified by some of the major initiatives that NCI undertook to reduce smoking among Americans:

1. In 1988, the Community Intervention Trial for Smoking Cessation (COMMIT) provided persistent tobacco cessation messaging through community mobilization, and resulted in modest increases in cessation rates among light-to-moderate smokers (17,18);
2. In 1991, the American Stop Smoking Intervention Study (ASSIST) deployed policy-based approaches to prevent and reduce tobacco use; 17 states that implemented ASSIST had a greater decrease in adult smoking prevalence than states that did not implement the intervention (19); and
3. In 2011, the State and Community Tobacco Control (SCTC) Research Initiative promoted innovative research that benefits state and community tobacco control efforts. Areas of research included secondhand smoking, tobacco tax and pricing, and tobacco industry marketing and promotion (20).

The Smokefree.gov Initiative, created and managed by the Tobacco Control Research Branch of NCI, is currently in its 17th year and provides free and evidence-based assistance to smoking cessation through online and smartphone-based resources.

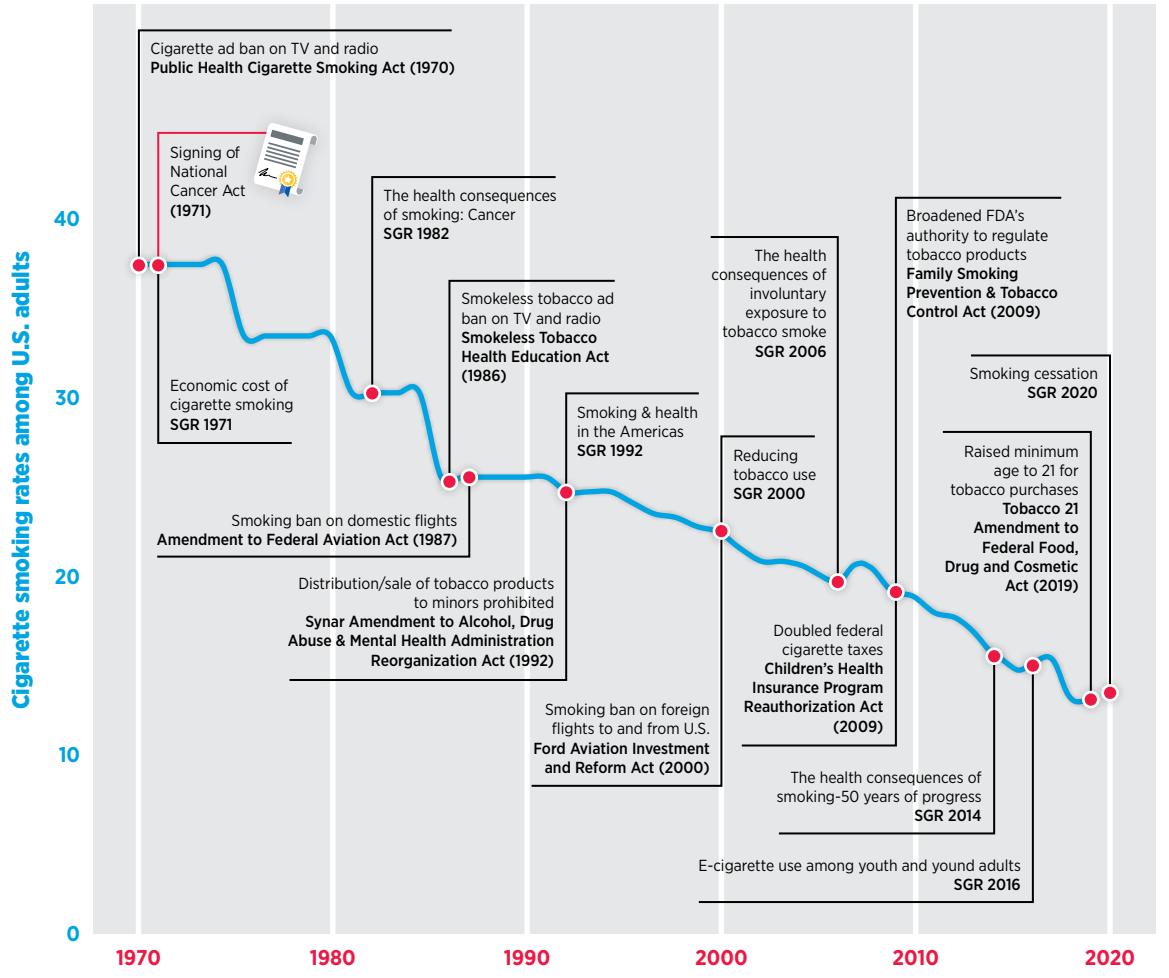
Implementation of nationwide public education campaigns, as well as comprehensive tobacco control policies, has resulted in a significant decrease in the U.S. smoking rates from 37.4 percent in 1971 to 14 percent in 2019 (12,21–23) (see **Figure 3**, p. 14). As a result, far fewer Americans are dying from lung cancer today than did just two decades ago (24). During 2011-2017, the latest

Successful efforts to **reduce smoking rates** among Americans have resulted in a **41 percent decline in lung cancer-related deaths** from 1991 to 2018 (4).

FIGURE 3

NATIONAL CANCER ACT
50 YEARS
1971-2021

REFLECTING ON FIVE DECADES OF POLICIES AND LEGISLATION AGAINST TOBACCO USE



Since the publication of the landmark 1964 Surgeon General's report on smoking (10), all stakeholders in the medical research community have played pivotal roles in advocating for policies that have had a tangible and direct impact on public health. As shown by the blue line, there has been a steady decline in smoking rates from 37.4 percent in 1970 to 14 percent in 2019, which amounts to a more than 60 percent decline over this time period (12). Major federal laws and key Surgeon General's Reports (SGR) raising public awareness about the health hazards of smoking are indicated (red dots).

time period for which such data are available, nearly 10 percent more Americans were surviving five years or longer after lung cancer diagnosis compared to 1975-1977 (3). The sharp decline in lung cancer deaths in the last two decades also parallels the unprecedented pace of discoveries in basic and translational research leading to clinical breakthroughs against lung cancer.

Landmark Discoveries Fueling Advances in Lung Cancer Diagnosis and Treatment

Like most other cancers, mechanisms underlying the onset and progression of lung cancer are complex and heterogeneous (25). Breakthrough discoveries decoding the initiation and progression of lung cancer have provided valuable insights

THE HONORABLE

Dianne Feinstein

U.S. Senator for California

"As we mark the 50th anniversary of the National Cancer Act, we honor the millions of Americans who have been touched by cancer, including those not with us today. The search to find a cure for cancer is a mission that should unite us all, and one pathway toward that cure is to continue to invest in critical research to finally conquer the more than 100 diseases we refer to as cancer."

THE HONORABLE

Brian Fitzpatrick

U.S. Representative for Pennsylvania's 1st District

Co-Chair, Congressional Cancer Caucus

"I am proud to join the American Association for Cancer Research in commemorating the 50th anniversary of the National Cancer Act, which declared war on cancer and paved the way for world-class cancer care and research. As Co-Chair of the Congressional Cancer Caucus and author of the Fairness to Kids with Cancer Act, I applaud the work being done across the country to support our citizens battling this deadly disease. Cancer is a disease that knows no boundaries, and now is the time to continue our fight to get Americans the care and lifesaving treatments that they need."

into early detection and treatment. Early detection among individuals who are at a high risk of developing lung cancer, primarily due to tobacco use, is saving lives (see **Screening for Early Detection**, p. 55) (26). Basic research discoveries have taught us that lung cancers are driven by alterations, also referred to as mutations (see sidebar on **Genetic Mutations**, p. 30), in several key genes, such as the oncogenic rat sarcoma (RAS) (27–32), Epidermal Growth Factor Receptor (EGFR) (33–35), Fibroblast Growth Factor Receptor (FGFR) (36), Anaplastic Lymphoma Kinase (ALK) (37,38), c-ros oncogene 1 (ROS1) (39), Rearranged during Transfection (RET) (38,40–42), Mesenchymal-Epithelial Transition factor (MET) (43,44), and Neurotrophic Tropomyosin Receptor Kinase (NTRK) (45), among others. Alterations in these genes allow cancer cells to grow unchecked and evade cell death (46). Molecular characterization of the lung cancer genome has highlighted the diversity of genetic alterations present in the disease. These findings have provided important mechanistic insights into lung cancer biology and have fueled the development of a class of highly effective anticancer treatments known as molecularly targeted therapeutics.

In addition to the discoveries that uncovered the genetic and epigenetic underpinnings of lung cancer, decades of basic research in immunology have led to the identification of immune checkpoint proteins, including PD-1 and CTLA-4, that function as "brakes" on T cell activation and can help cancer cells evade destruction by the immune system (47–49) (see **Releasing the Brakes on the Immune System**, p. 107). This knowledge has resulted in the development of a class of immunotherapeutics, known as the immune checkpoint inhibitors, that relieve suppression of a patient's immune system by cancer cells, thus allowing T cells to attack and eliminate cancer cells (50). Treatment with immune checkpoint inhibitors has yielded remarkably durable responses for many patients with lung cancer (51).

The transformation in the lung cancer treatment landscape has been staggering during just the past decade. In 2010, there were only three FDA-approved molecularly targeted therapeutics—gefitinib (Iressa) and erlotinib (Tarceva) directed against just one molecular target, EGFR, and bevacizumab (Avastin), an angiogenesis inhibitor—to treat patients with lung cancer (52). As of July 31, 2021, 30 agents—molecularly targeted therapeutics and immune checkpoint inhibitors—have been approved by FDA to treat various subtypes of lung cancer (52–54) (see **Figure 4**, p. 16). These treatment options include additional molecularly targeted therapeutics against EGFR and its specific mutated forms, as well as targeted therapeutics against a myriad of additional molecules such as ALK, ROS, MET, RET, NTRK, and one variant of the historically intractable target KRAS (G12C).

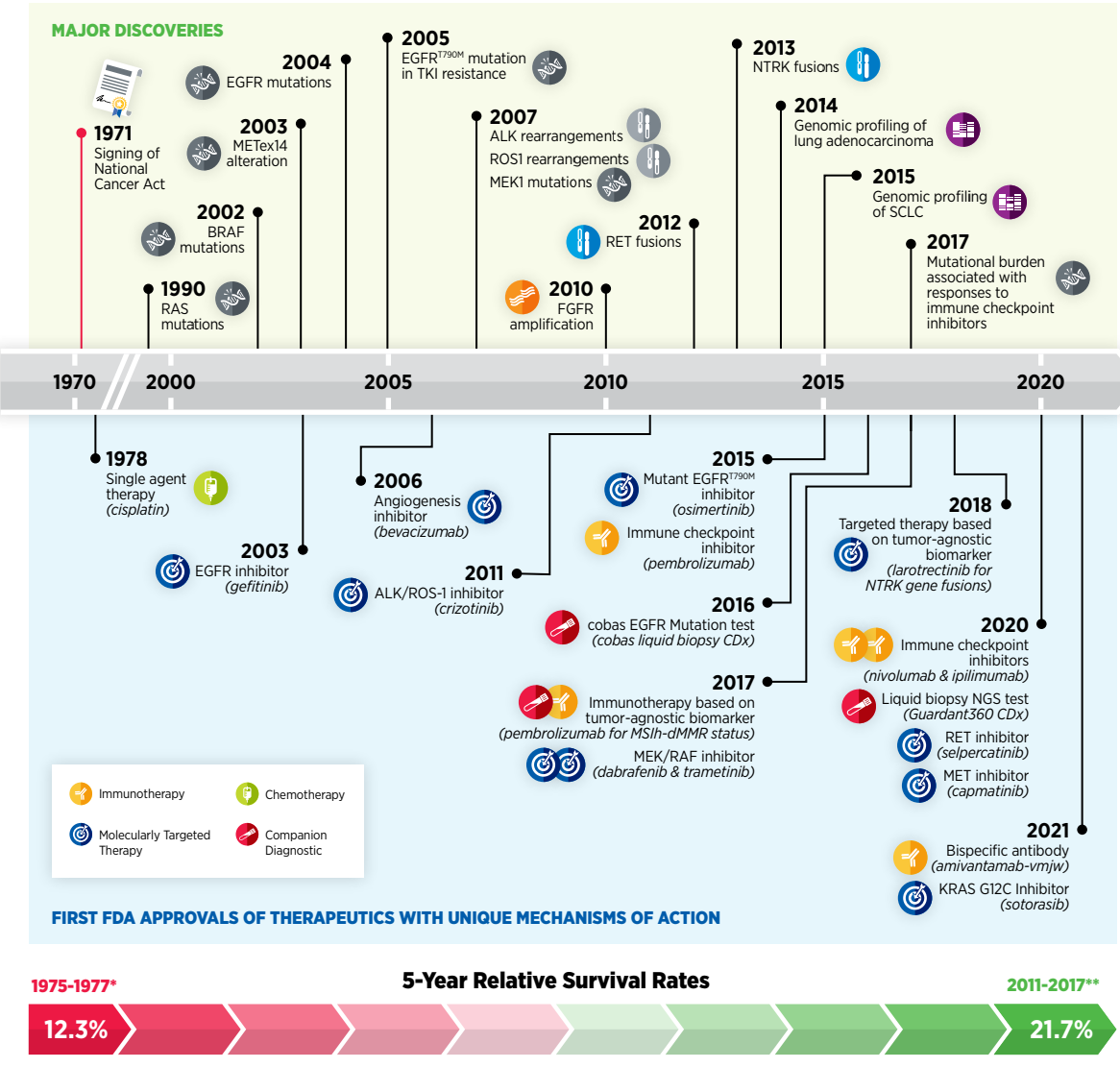
Identification of cellular and molecular alterations that drive lung cancer development has led to the discovery of numerous biomarkers (see **Figure 4**, p. 16), which are foundational to the development of companion diagnostic tests for cancer treatment. Companion diagnostic tests guide treatment decisions by determining whether specific cellular or molecular characteristics, such as genetic alterations, are present in a patient's lung cancer (55). In 2020, FDA approved the first companion diagnostic test that combines two cutting-edge technologies, known as next-generation sequencing and liquid biopsy, to identify cancer-driving alterations in the blood derived from patients with non–small cell lung cancer (NSCLC) to decide what treatment may be most effective (56).

Rapid advances in the field of molecularly targeted therapeutics and immunotherapeutics have improved the outcomes for patients with several cancer types beyond lung cancer. As one example, progress made against metastatic lung cancer has been mirrored by equally impressive advances

FIGURE 4

NATIONAL CANCER ACT
50 YEARS
1971-2021

50 YEARS OF PROGRESS AGAINST LUNG CANCER



5-Year Relative Survival Rates

1975-1977*: 12.3%

2011-2017**: 21.7%

* Based on data available at: https://seer.cancer.gov/archive/csr/1975_2017/

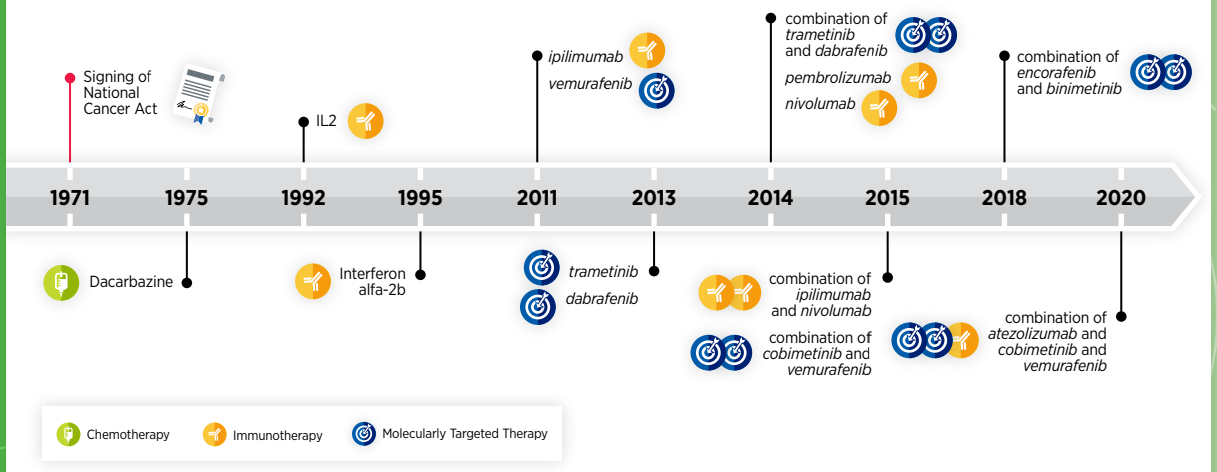
** Based on data available at: https://seer.cancer.gov/statfacts/html/lungb.html

Publication of the first draft of a human genome in 2001 has revolutionized the field of cancer genomics and accelerated the era of precision medicine. Identification of key drivers of lung cancer in the mid-2000s fast-tracked target discovery and resulted in development of a myriad of molecularly targeted therapeutics and immunotherapeutics that have contributed to an increase in 5-year survival rates for lung cancer patients in the past 50 years by nearly ten percentage points (as depicted by a red-to-green arrow). Also indicated on the timeline are major advances in target discovery (top), closely followed by development of a molecularly targeted therapeutic and/or immunotherapeutic, as well as companion diagnostics to inform treatment decisions (bottom). Note: The bottom panel of the timeline focuses on the first FDA approval of a molecularly targeted therapeutic or immunotherapeutic with a unique mechanism of action. Additional therapeutics with similar mechanisms of action have been approved for lung cancer in subsequent years. As of July 31, 2021, a total of 30 agents (molecularly targeted therapeutic or immunotherapeutic) have been approved by FDA to treat various subtypes of lung cancer. Major advances in cancer immunotherapy are discussed elsewhere in the report (see **Figure 23**, p. 109). TKI stands for tyrosine kinase inhibitor. See text for details and references.

FIGURE 5

NATIONAL CANCER ACT
50 YEARS
1971-2021

50 YEARS OF RESEARCH-DRIVEN THERAPEUTIC ADVANCES AGAINST MELANOMA



Melanoma is the deadliest form of skin cancer. According to the most recent estimates, incidence of melanoma in the U.S. will more than double by 2040, making it the second most common cancer (58). Until 2000, the standard of care for patients with metastatic melanoma was a cytotoxic 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, 2021, the U.S. Food and Drug Administration (FDA) approved four 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), and pembrolizumab (Keytruda). 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). The March 2011 approval of ipilimumab came after the immunotherapeutic was shown to be the first treatment ever to extend survival for patients with this deadly disease (59). Together, these innovative new therapeutics have helped accelerate the decline in melanoma-related deaths both among males (5.7 percent per year between 2013 and 2018) and females (4.4 percent per year between 2012 and 2018) (57). Importantly, the 5-year relative survival rate for individuals diagnosed with metastatic melanoma has increased from 18 percent (2006-2012) (60) to 30 percent (2011-2017, the most recent time period for which these data are available) (4). Note that this timeline focuses on systemic treatments for metastatic melanoma; other therapeutics have been approved for the prevention of disease recurrence or the treatment of localized lesions.

against metastatic melanoma, the deadliest form of skin cancer. Research-driven discoveries have contributed to the development and approval of innovative new treatments for patients with melanoma (see **Figure 5**, p. 17), leading to a steady decline in the melanoma death rate, which has fallen by more than 5 percent every year from 2013 to 2018, the most recent year for which such data are available (4,57).

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

Despite the unprecedented progress against cancer since the signing of the National Cancer Act (2), the disease continues to be a leading cause of death in the United States and around the

world (3,61). In the United States, an estimated 1,898,160 new cancer cases and 608,570 deaths from the disease are projected in 2021 alone (3) (**Table 1**, p. 19). These numbers translate into approximately 18 new patients diagnosed with cancer, and nearly six patients dying from cancer, every five minutes.

Since its onset in early 2020, the Coronavirus Disease 19 (COVID-19) pandemic has further hampered our advances against cancer by negatively impacting all aspects of cancer science and medicine. While the full impact of COVID-19 on cancer research and care is yet to be determined, evidence for adverse effects of the pandemic across the continuum of cancer science and medicine is rapidly accruing. These adverse effects include decreased productivity and lost career opportunities among cancer researchers, in particular, among early-stage, minority, and female investigators because of the closures of and restricted access to research institutes (62); refocused expertise and resources by some cancer researchers to study severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which causes COVID-19 (63); considerably reduced research funding by nonprofit cancer societies (62), which typically contribute up to 50 percent of all cancer research funding in the United States (64); substantially reallocated financial resources by many health care systems away from cancer care to address the challenges imposed by the COVID-19 pandemic (65–67); disruption in cancer screening, diagnosis, and treatment; and a significant decline in clinical trial enrollment and conduct (63,68,69).

THE HONORABLE

Adriano Espaillat

U.S. Representative for New York's 13th District

"In the 50 years since the National Cancer Act was signed into law, our federal commitment to the prevention, detection, diagnosis, and treatment of cancers has yielded breakthrough therapies and interventions to positively impact the lives of millions of cancer patients and their families across the United States and around the world. Breakthroughs that we have seen in the continuum of care from cancer research to treatment – especially focused on addressing cancer health disparities in African American and Latino populations – gives me great confidence that our federal investment in research through the National Institutes of Health and the National Cancer Institute will continue to yield positive and constructive impacts on the lives of cancer patients and their loved ones."

There are also serious concerns about the higher burden of COVID-19 for patients with cancer. Multiple studies indicate that cancer patients are at a greater risk of COVID-19 infection and mortality (70–79). This risk is the highest for patients with lung cancer and hematological malignancies and among patients from certain underserved population groups (79–87) (see sidebar on **COVID-19 in Patients With Cancer**, p. 20). A comprehensive overview of the impact of COVID-19 on cancer research and patient care will be presented in a separate AACR report to be released in early 2022.

VARIABLE PROGRESS AMONG TYPES OF CANCER AND STAGES OF DIAGNOSIS

Cancer is a heterogeneous disease, and because of that, progress against cancer has not been uniform across different types of cancer or for all stages of a given cancer type (88,89).

A key indicator of these challenges is the 5-year relative survival rate, which varies widely depending on the cancer type and stage (3). For example, there are striking differences between 5-year relative survival rates for breast (female) cancer and melanoma compared to pancreatic and liver cancers. For those diagnosed between 2011 and 2017, the most recent time frame for which such data are reported, 90 percent of patients diagnosed with breast cancer and 93 percent of those diagnosed with melanoma were surviving five years or more. In comparison, during the same time period, only 11 percent of patients diagnosed with pancreatic cancer and 20 percent of patients diagnosed with liver cancer survived five years or more (3).

Five-year relative survival rates also differ drastically for patients with a given type of cancer, depending on how advanced their cancer is at the time of diagnosis. As an example, women who are diagnosed with breast cancer that is still confined entirely to breast tissue (i.e., early-stage or localized breast cancer) have a 99 percent 5-year relative survival rate. By contrast, only 29 percent of women who are diagnosed when breast cancer has already spread to other organs and tissues in the body (i.e., late-stage or distant breast cancer) live five years or more after diagnosis (3). Similarly, 5-year relative survival rates for men diagnosed with localized versus distant prostate cancer are greater than 99 percent versus 31 percent, respectively (3). These statistics point to the critical need of developing new, effective, and when possible, minimally invasive tests (see **Figure 13**, p. 59) that can detect cancer at the earliest possible stage, when treatments are more likely to be curative. Furthermore, concerted efforts to increase the uptake of routine cancer screening among eligible populations (see **Screening for Early Detection**, p. 55) and to enhance the adoption of preventive measures that can reduce the risk of cancer (see **Preventing Cancer: Identifying Risk Factors**, p. 36) can substantially reduce the burden of cancer in coming years.

TABLE 1

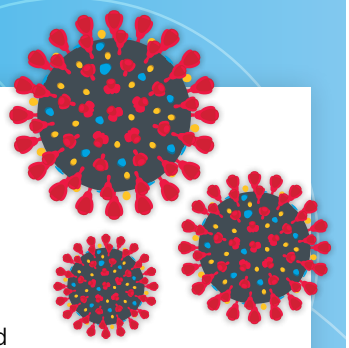
ESTIMATED INCIDENCE AND MORTALITY FOR SELECTED CANCERS*

	ESTIMATED 2021 INCIDENCE			ESTIMATED 2021 DEATHS		
	Total	Male	Female	Total	Male	Female
All Sites	**1,898,160**	**970,250**	**927,910**	**608,570**	**319,420**	**289,150**
Head and Thorax Region						
Brain & other nervous system	24,530	13,840	10,690	18,600	10,500	8,100
Eye & orbit	3,320	1,750	1,570	400	220	180
Tongue	17,960	13,040	4,920	2,870	1,930	940
Mouth	14,290	8,400	5,890	2,650	1,520	1,130
Pharynx	18,470	14,990	3,480	3,870	3,060	810
Other oral cavity	3,290	2,370	920	1,460	1,110	350
Larynx	12,620	9,940	2,680	3,770	3,020	750
Lung & bronchus	235,760	119,100	116,660	131,880	69,410	62,470
Breast	284,200	2,650	281,550	44,130	530	43,600
Gastrointestinal (GI) System						
Esophagus	19,260	15,310	3,950	15,530	12,410	3,120
Stomach	26,560	16,160	10,400	11,180	6,740	4,440
Liver & intrahepatic bile duct	42,230	29,890	12,340	30,230	20,300	9,930
Gallbladder & other biliary	11,980	5,730	6,250	4,310	1,770	2,540
Pancreas	60,430	31,950	28,480	48,220	25,270	22,950
Small intestine	11,390	6,130	5,260	2,100	1,110	990
Colon and rectum	149,500	79,520	69,980	52,980	28,520	24,460
Anus, anal canal, & anorectum	9,090	3,020	6,070	1,430	560	870
Endocrine System						
Thyroid	44,280	12,150	32,130	2,200	1,050	1,150
Urogenital System						
Kidney & renal pelvis	76,080	48,780	27,300	13,780	8,790	4,990
Ovary	21,410		21,410	13,770		13,770
Penis and other genital organs, male	2,210	2,210		460	460	
Prostate	248,530	248,530		34,130	34,130	
Testis	9,470	9,470		440	440	
Uterine cervix	14,480		14,480	4,290		4,290
Uterine corpus	66,570		66,570	12,940		12,940
Urinary bladder	83,730	64,280	19,450	17,200	12,260	4,940
Vulva	6,120		6,120	1,550		1,550
Vagina and other genital organs, female	8,180		8,180	1,530		1,530
Skin (excluding basal & squamous)						
Melanoma-skin	106,110	62,260	43,850	7,180	4,600	2,580
Other nonepithelial skin	9,210	5,860	3,350	4,360	3,060	1,300
Hematalogical System						
Acute lymphocytic leukemia	5,690	3,000	2,690	1,580	900	680
Chronic lymphocytic leukemia	21,250	13,040	8,210	4,320	2,620	1,700
Acute myeloid leukemia	20,240	11,230	9,010	11,400	6,620	4,780
Chronic myeloid leukemia	9,110	5,150	3,960	1,220	680	540
Other leukemia	4,800	3,110	1,690	5,140	3,080	2,060
Hodgkin lymphoma	8,830	4,830	4,000	960	570	390
Non-Hodgkin lymphoma	81,560	45,630	35,930	20,720	12,170	8,550
Myeloma	34,920	19,320	15,600	12,410	6,840	5,570
Other Cancers						
Bones & joints	3,610	2,100	1,510	2,060	1,190	870
Soft tissue (including heart)	13,460	7,720	5,740	5,350	2,840	2,510

*Rounded to the nearest 10.

Source: Estimated new cases are based on 2003-2017 incidence rates reported by the North American Association of Central Cancer Registries (NAACCR). Estimated deaths are based on 2004-2018 US mortality data, National Center for Health Statistics, Centers for Disease Control and Prevention. (3)

COVID-19 IN PATIENTS WITH CANCER



The COVID-19 pandemic has disrupted all facets of life across the globe. Evidence is emerging on how patients and survivors of cancer have been impacted by the pandemic. Cancer patients often have weakened immune systems because of the type of cancer they have and/or the treatment they receive. A compromised immune system places patients with cancer at a particularly high risk of infection and death from COVID-19. The true burden of the pandemic on cancer patients and survivors will likely become clearer in coming years with more systematic studies. Here, we are highlighting some recent studies that report the incidence and outcomes of COVID-19 among cancer patients. Known effects of the pandemic on other aspects of cancer research and care, such as screening and treatment, are discussed elsewhere in this report:

TWICE as likely	Patients with cancer were, on average, **twice as likely to die** from COVID-19 infection (70).
7 TIMES more likely	Patients who were recently diagnosed with cancer were at a **7 times higher risk of COVID-19 infection** (80).
Most **VULNERABLE**	Patients with lung cancer or hematological malignancies were at a significantly **higher risk of COVID-19 infection and death**, compared to patients who had other cancer types (72,79,81,83–87).
More than **5 TIMES**	Black women with a recent breast cancer diagnosis had **more than 5 times higher risk of developing COVID-19 infections** than white patients (80).

DISPARITIES IN PROGRESS FOR CERTAIN U.S. POPULATION GROUPS

Cancer affects all people, but certain segments of the U.S. population with social, environmental, and economic disadvantages experience a disproportionate burden of cancer (see sidebar on **Which U.S. Population Groups Experience Cancer Health Disparities?**, p. 21).

The NCI defines cancer health disparities as adverse differences in cancer experienced by certain segments of the U.S. population, 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 (see sidebar on **U.S. Cancer Health Disparities**, p. 22).

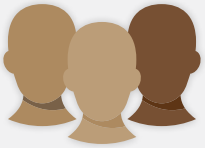
Considerable progress has been made in documenting cancer disparities over the past two decades, which in turn has informed policies to address these inequalities (see **Addressing Cancer Health Disparities**, p. 150) (91,98–100). There are also some encouraging signs of narrowing disparities, as evidenced by declining cancer incidence and mortality rates among underserved population groups. During 2008–2017, the most recent period for which such data are available, the overall cancer incidence rates decreased faster among African American males (2.3 percent per year) compared to white males (1.7 percent per year). Cancer mortality also declined faster among African Americans than whites for both males (2.7 percent versus 1.7 percent per year) and females (1.6 percent versus 1.3 percent per year) (92). Despite these improvements, the burden of cancer is still substantially higher for racial and ethnic minorities and other underserved populations (91,98,101,102). Unfortunately, the COVID-19 pandemic has further disrupted the progress made against cancer disparities (80).

Cancer health disparities pose significant challenges, with long-term societal and economic ramifications for individuals and

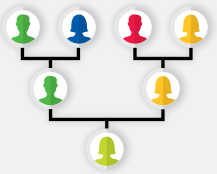
WHICH U.S. POPULATION GROUPS EXPERIENCE CANCER HEALTH DISPARITIES?

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 U.S. population groups (90) including:

Racial and ethnic minority groups



Individuals of different ancestry



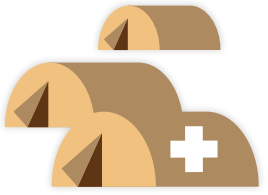
Individuals of low socioeconomic status

Individuals with disabilities

Individuals who lack or have limited health insurance coverage

Residents in certain geographic locations, including rural areas

Refugees or asylum seekers

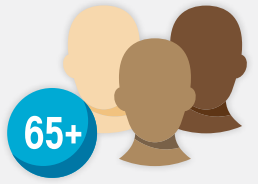


Immigrants

Members of the lesbian, gay, bisexual, and transgender community

Adolescents and young adults (AYA)

Elderly



the entire nation. It is critical that all stakeholders in the medical research community work together to identify and eliminate the structural and systemic injustices that prevent health equity for the underserved groups of the U.S. population. The *AACR Cancer Disparities Progress Report 2020* summarizes current knowledge of the complexities that we must overcome to address cancer health disparities and identifies key areas where progress can, and must, be made (91) (see sidebar on **Why Do U.S. Cancer Health Disparities Exist?**, p. 23).

THE GROWING BURDEN OF CANCER

The burden of cancer is growing rapidly in the United States and worldwide. According to the latest estimates from the World Health Organization (WHO), cancer was the first or second leading cause of death before the age of 70 in 112 out of 183 countries in 2019 (103). In the United States, researchers estimate that the number of new cancer cases will exceed 2.2 million and the number of cancer deaths will reach nearly 900,000 by the year 2040 (3,61). Overcoming the burdens posed by cancer necessitates developing and implementing effective strategies across the continuum of cancer research and care.

The anticipated sharp increases in the number of new cancer cases and cancer deaths reflect both the projected overall population growth and the expected increase in the population that is age 65 or older. Cancer is primarily

U.S. CANCER HEALTH DISPARITIES

Certain population groups in the U.S. (see sidebar on **Which U.S. Population Groups Experience Cancer Health Disparities?**, p. 21) shoulder a disproportionate burden of cancer. Some recent examples of disparate cancer incidence, death, 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 ***The AACR Call to Action***, is included in the inaugural ***AACR Cancer Disparities Progress Report 2020*** (91).

More than **TWICE**	The **incidence of multiple myeloma is more than twice** in African Americans compared to non-Hispanic whites (92).
More than **4 TIMES**	American Indian/Alaskan Native individuals living in Alaska are **more than 4 times more likely to develop stomach cancer** compared to whites (93).
35% increase	During 2012–2016, the **incidence of early-onset colorectal cancer increased 35 percent** for those living in rural areas, compared to less than 20 percent among those living in urban areas (94).
More than **DOUBLE**	The **rate of cancer diagnoses is more than double** among transgender men compared to cisgender men (95).
More than **12% HIGHER**	From 2007 to 2011, **overall age-adjusted cancer mortality was 12.3 percent higher** in the U.S. counties where poverty was persistent (i.e., 20 percent or more residents were living in poverty since 1980), compared to counties where poverty was not persistent (96).
More than **DOUBLE**	Women in Missouri with no health insurance have **more than double the likelihood of being diagnosed with breast cancer** at a late stage, compared to women who are privately insured (97).

a disease of aging. Individuals who are age 65 and older account for 54 percent of new cancer diagnoses (4), and this population in the United States is expected to grow from 56 million in 2020 to 82.7 million in 2045 (104).

Substantial progress has been made toward reducing cancer incidence in the United States; new cancer cases have declined 13 percent from their peak in 1992 to 2018, the year for which the most recent data are reported (4). However, overall cancer incidence has been rising among the AYA population (ages 15 to 39), which has seen nearly a 30 percent increase in cancer incidence from 1973 to 2015 (105). In addition, the incidence of certain cancer types is on the rise specifically among people younger than 50 (106,107). As one example, a recent study has reported that new cases of esophageal cancer increased among people younger than 50 nearly three percent every year between 1975 and 2015 (108). This is especially concerning because esophageal cancers among this population were detected at more advanced stages

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. The factors contributing to differences or inequalities include:

Social factors

- Education
- Income
- Employment
- Health literacy

Clinical factors

- Access to health care
- Quality of health care

Psychological factors

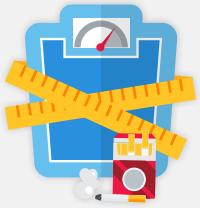
- Stress
- Mental health

Cultural factors

- Cultural beliefs
- Cultural health beliefs

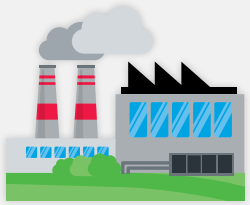
Behavioral factors

- Tobacco use
- Diet
- Weight
- Physical activity
- Adherence to cancer screening and vaccination recommendations



Environmental factors

- Air and water quality
- Transportation
- Housing
- Community safety
- Access to healthy food sources and spaces for physical activity



Genetic and biological factors

General health

- Infection with certain pathogens, such as human immunodeficiency virus (HIV)
- Having other health conditions, e.g., diabetes

Adapted from (91).

(84.9 percent) compared to those detected among patients older than 50 (67.3 percent). Another alarming trend is that new cases of colorectal cancer among individuals younger than 50 have been rising since 2007, and the increases are especially high among American Indians/Alaska Natives and non-Hispanic whites (109). These trends of early-onset colorectal cancer have prompted U.S. Preventive Services Task Force (USPSTF), as well as some cancer-focused professional societies and organizations, to update existing guidelines recommending that screening for colorectal cancer start at an earlier age (see sidebar on **Consensus Cancer Screening Recommendations**, p. 63).

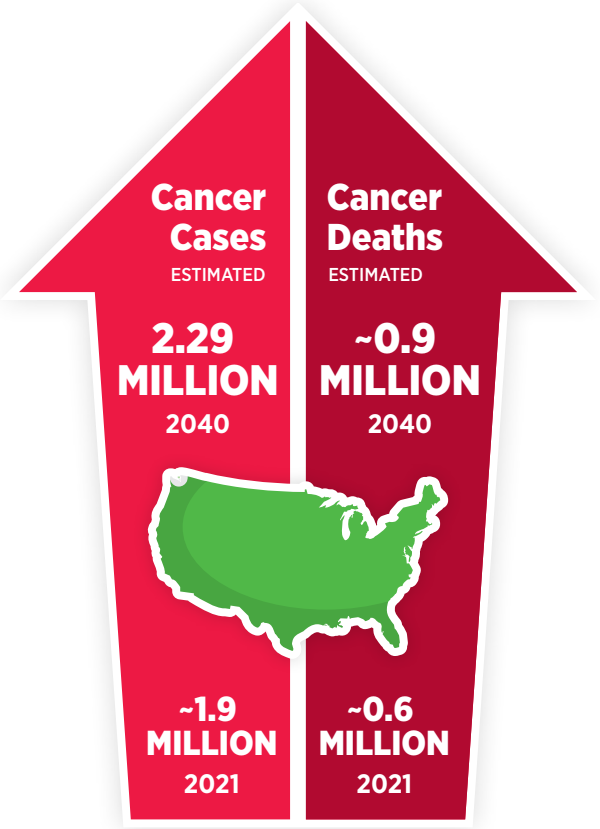
THE GLOBAL CHALLENGE OF CANCER

Beyond the United States, the burden of cancer is growing rapidly across the globe. According to the latest estimates from World Health Organization (WHO), cancer was the first or second leading cause of death before the age of 70 in 112 out of 183 countries in 2019 and accounted for nearly 10 million deaths worldwide in 2020 (61). Notably, the global burden of cancer is predicted to rise significantly in the coming decades unless new and more effective approaches to cancer prevention, early detection, and treatment are developed and successfully implemented across the globe. The estimated increase in the global burden of cancer will

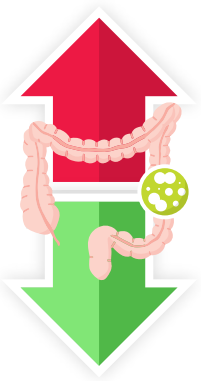
be fueled by overall population growth and expansion in the segment of the world's population most likely to develop cancer, i.e., those age 65 and older.

Cancer health disparities around the world are highlighted by the widely different cancer incidence and mortality rates across regions. As an example, low- and middle- income countries (LMICs) experienced a disproportionately higher burden of cancer and, in fact, shouldered 65 percent of all global cancer deaths in 2020 (110) even though only 56 percent of new cancer cases occurred in these countries (see sidebar on **Cancer: A Global Public Health Challenge**, p. 25).

The global disparities in the cancer burden largely reflect differences in exposure to risk factors, as well as the barriers to high-quality cancer prevention and early detection in countries with limited resources. For example, it is estimated that the implementation of effective vaccination intervention will lead to the near elimination of HPV-related cervical cancer, in highly developed countries, such as Australia by the end of this decade (114). However, most low-income countries with high cervical cancer incidence will not achieve this target even by the end of this century (115). In addition, low-income countries have had little to no access to the numerous cutting-edge diagnostic and anticancer therapeutic agents that have been approved by Food and Drug Administration (FDA) in the United States. One area in which progress is urgently needed is addressing the disparities in the conduct of cancer clinical trials which are vital for the development of new anticancer therapeutics. A recent analysis of contemporary cancer clinical trials across the globe showed



INCIDENCE OF COLORECTAL CANCER



Age <50
2.3% increase
every year (2014-2018)

Age 65+
3.1% decrease
every year (2014-2018)

that only eight percent of such studies were led by LMICs (116). These inequities limit our ability to reduce the global burden and suffering due to cancer.

Given the profound adverse impact of cancer on public health worldwide, it is imperative that the international biomedical research community work together to drive down cancer incidence and mortality and mitigate the global cancer inequities. In this regard, NCI established the Center for Global Health 10 years ago. The priorities of the center include supporting innovative, impactful research that addresses key scientific issues in global cancer control; supporting global cancer research training, particularly in LMICs, which enables global scientific collaboration; and promoting the

THE HONORABLE
Roy Blunt

U.S. Senator for Missouri

Ranking Member, Senate Appropriations Subcommittee on Labor, Health and Human Services, Education, and Related Agencies

"Federal investment in the National Institutes of Health has provided hope to millions of Americans and their families dealing with cancer. Over the past six years, we have worked in a bipartisan way to increase NIH funding by nearly 43%, providing a 32% increase for the National Cancer Institute, and a focused funding stream to increase the number of cancer grants. With major advances in leukemia, prostate, breast, and lung cancer treatments, this is the most exciting time for cancer research in decades. As the top Republican on the committee that funds NIH, I'll continue to be a vocal advocate for federal investments in lifesaving medical research."

CANCER: A GLOBAL PUBLIC HEALTH CHALLENGE

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 burden of cancer also highlights key barriers to achieving global health equity, as indicated by the vast disparities between countries with low, medium, high, and very high human development index (HDI)[a]. The following examples offer a broad view of the global burden of cancer.

New Cases

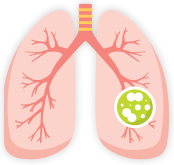
19.3 million in 2020[b]; projected to increase 47 percent to 28.4 million in 2040.

Cancer Deaths

One in 6 of all deaths worldwide is attributable to cancer. According to World Health Organization (WHO) estimates for 2019, cancer is the first or second leading cause of death before the age of 70 in 112 out of 183 countries (103).

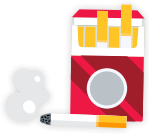
Lung Cancer

Lung cancer was the most diagnosed cancer worldwide until 2018 (2 million or 11.6 percent of all new cancer cases in 2018) (111). It remains the leading cause of cancer-related deaths (1.8 million or 18 percent of all estimated cancer-related deaths in 2020[b]). Nearly 62 percent (1.1 million) of these deaths are estimated to occur in Asia.



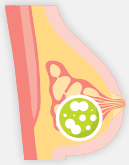
Tobacco Use

Tobacco use continues to be the major preventable cause of death from cancer worldwide. In 2018[b], tobacco use was responsible for 25 percent of all cancer deaths globally (103).



Breast Cancer

Breast cancer (2.3 million female breast cancers, which make up 11.7 percent of all new cancer cases) surpassed lung cancer (2.2 million or 11.4 percent of all new cases for both sexes combined) in 2020[b] as the type of cancer most diagnosed worldwide.



Disparities

The projected increase in cancer incidence from 2020 to 2040 is estimated to be more pronounced in countries with low and medium HDI, 95 percent and 64 percent respectively, compared to countries with high and very high HDI, 56 percent and 32 percent respectively.

[a] Human Development Index (HDI): A composite metric of human development in key areas of life—education, life expectancy, and per capita income—used by the United Nations Development Programme's Human Development Report Office (112). HDI is sometimes used interchangeably with The World Bank classification of countries into low income, low middle income, upper middle income, and high income countries based on Gross National Income per capita (113).

[b] The indicated years are the most recent years for which the included data are available.

Developed using data from (61).

integration of current scientific knowledge while engaging NCI with other key partners in global cancer control (117). Notably, 13 percent of NCI's extramural support in 2020 included international components, compared to only nine percent in 2010, while 32 percent of its international awards involved LMICs (110). Through a robust future scientific strategy that focuses on technologies for global cancer control, global cancer implementation science, global cancer health disparities, cancer clinical trials in LMICs, and understanding cancer etiology and biology through global collaborations, NCI aims to catalyze new discoveries to reduce the global incidence, morbidity, and mortality from cancer (110).

Funding Cancer Research: A Vital Investment

The enormity of the challenges posed by cancer on the U.S. health and economy underscores the urgent need for more investments in cancer science and medicine. Investment in cancer research not only benefits all Americans through new discoveries that save lives, but also creates jobs that boost local economies across the nation.

The toll of cancer that is experienced by patients, their caregivers, friends, and family can never be quantified in dollar amounts. It is possible, however, to estimate the direct and

indirect economic impact of cancer on the society as a whole. Cancer patients in the United States paid $5.6 billion out of pocket for cancer treatments in 2018 (118), which is nearly the same as the total $6 billion NCI funding for cancer research that year (119). Furthermore, an estimated $200.7 billion of total U.S. health care was spent on cancer-related health care in 2020 (120). That number is projected to increase to $245.6 billion by 2030, which amounts to a 22.4 percent increase. These costs do not reflect the additional indirect economic burden weathered by the patients and their caregivers in lost earnings, and by employers in lost productivity (121). In addition, these financial burdens of cancer collectively contribute to cancer health disparities (121). It is projected that the adverse impact of the COVID-19 pandemic on cancer screening, diagnosis, and treatment will compound the already enormous toll of cancer (3,122).

The year 2021 marks the 50th anniversary of the National Cancer Act that was signed into law by President Richard M. Nixon (2). The National Cancer Act has catalyzed research across the continuum of cancer science and medicine. This year also marks the 20th anniversary of the publication of the human genome (123), which has accelerated the development of precision medicine, and the 10th anniversary of the annual *AACR Cancer Progress Report* (124), which has chronicled the remarkable progress against cancer over the past decade. The unprecedented advances, highlighted in the current report and the ten prior editions, underscore how cross-disciplinary research has been vital in accelerating the pace of scientific innovation and emphasize the importance of public education and advocacy in our progress against cancer (see **Investing in a Healthier Future Through Research**, p. 139). Importantly, fundamental discoveries that have led to developing effective approaches to preventing, detecting, and treating cancer would not have been possible without the public funding of cancer research through NIH and NCI. Increasing in our investments now will ensure that we prevent cancer incidence, morbidity, and mortality in the years and decades to come. Therefore, it is imperative that Congress continue to increase its investment, in a consistent and predictable manner, in federal agencies, including NIH, NCI, FDA, CDC, and Department of Defense (DoD), that are essential for turning discovery science into lifesaving care for all (see **The AACR Call to Action**, p. 154).

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; cancers in about 10 percent of patients contain inherited mutations.
- Cancer initiation and progression are strongly influenced by interactions among cancer cells and cellular and molecular factors in their environment, referred to as the tumor microenvironment.
- Each person's cancer is unique and so is the response to treatments; understanding why certain patients respond exceptionally well to treatments that are not effective for others is an elusive question in cancer medicine and an area of extensive ongoing investigation.
- The more we know about the contributions of the numerous individual genetic and other factors and their interplay in influencing cancer development among all populations, the more precisely and effectively we can prevent, diagnose, and treat cancer.

Discoveries across the breadth of medical research, from basic research to translational, clinical, and population science, have fueled our current understanding of cancer initiation and progression (see sidebar on **What Is Basic Research and How Does It Drive Progress Against Cancer?**, p. 28).

We now understand that cancer is not one disease but a collection of diseases that arise when the processes which control normal cell growth, division, and life span go awry. As a result, cells start to multiply uncontrollably, fail to die, acquire unique ways to obtain nutrients for survival, and begin to accumulate. In body organs and tissues, the accumulating cancer cells form masses called tumors, whereas in the blood or bone marrow they crowd out normal cells. Over time, some cancer cells may invade distant tissues, a process termed metastasis, by entering the bloodstream or the lymphatic system and form secondary tumors at remote sites. Most deaths from cancer are due to metastasis. Therefore, understanding the biological underpinnings of metastatic dissemination and identifying ways to prevent this process are key focus areas of ongoing research (127,128).

Cancer Development: Influences Inside the Cell

The normal behavior of each cell in the human body is controlled by its genetic material. The genetic material comprises chains of deoxyribonucleic acid (DNA), a complex molecule made up of four building blocks called bases. The four bases are organized in a very specific pattern to build two paired chains of the DNA. The DNA is packaged together with proteins called histones into condensed structures called chromosomes that are contained within a cell's nucleus (see sidebar on **Genetic and Epigenetic Control of Cell Function**, p. 29). Each person gets 23 chromosomes from each parent; thus, each normal cell has 46 chromosomes. The DNA is first converted into another complex molecule called ribonucleic acid (RNA), which is subsequently used by the cell to manufacture proteins. The order of the DNA bases and the way the DNA chains are packaged into chromosomes dictate which proteins and how much of them are made by each cell. Proteins are the molecules that perform important functions that dictate a cell's fate.

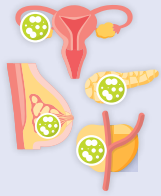
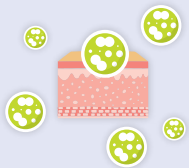
THE HONORABLE
Chris Murphy
U.S. Senator for Connecticut

"Cancer diagnoses turn people's lives upside down, and I'm grateful to organizations like the American Association for Cancer Research who are working to make the prevention, detection, diagnosis easier and more effective. I am proud to work alongside these efforts by pushing for bold investments in federal research that can transform our understanding of cancer."

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, however, has broad implications because it is fundamental to our understanding and treatment of human diseases, including cancer. The NIH spends more than half of its budget supporting basic research (125). NIH-supported basic research projects significantly contribute to novel target identification and drug development (126).

Selected examples of basic research discoveries and their transformative impact on cancer treatment are:

Basic Research	Clinical Advance	Current Status	
1960 Philadelphia chromosome is identified in patients with **chronic myelogenous leukemia (CML)**. **1987** Bcr-Abl protein is identified as a possible cause of CML.	**2001** The FDA approved imatinib, a targeted therapeutic against Bcr-Abl, for the treatment of patients with CML. **2006** Dasatinib is approved by FDA for the treatment of patients with CML who are resistant to imatinib.	**2021** There are four Bcr-Abl targeted therapeutics approved by FDA for the **treatment of patients with CML**.	
1977 PARP-1 protein is purified. **1990** BRCA1 gene is discovered. **1994** BRCA2 is discovered.	**2014** A PARP inhibitor, olaparib, is approved by FDA to treat women with **advanced ovarian cancer** who inherited a BRCA1/2 mutation.	**2021** There is at least one PARP-targeted therapeutic for the **treatment of breast, ovarian, pancreatic, and prostate cancers**.	
1984 HER2 gene is discovered.	**1998** Trastuzumab, the first targeted therapeutic against HER2 protein, is approved by FDA for the treatment of women with HER2-positive **metastatic breast cancer**.	**2021** HER2-targeted therapeutics are approved by FDA for the **treatment of breast and gastric (including gastroesophageal) cancers**.	
1989 VEGF-A, a regulator of normal and pathological angiogenesis and a major drug target, is identified.	**2004** VEGF-A targeted therapeutic, bevacizumab, is approved by the FDA for the **treatment of colorectal cancer**.	**2021** More than 10 antiangiogenic therapeutics have been approved by FDA to **treat multiple cancer types**.	
1992 PD-1 gene is discovered. **2000** Protein that binds to PD-1, PD-L1, is discovered.	**2014** First PD-1 targeted checkpoint inhibitor, pembrolizumab, is approved by FDA for **treatment of melanoma**.	**2021** Seven PD-1/PD-L1 targeted checkpoint inhibitors have been approved by FDA to **treat multiple cancer types**.	
1982 T cell receptor is discovered. **1984** T cell receptor is cloned.	**2017** The first chimeric antigen receptor (CAR) T-cell therapy is approved by FDA.	**2021** Five different **CAR T-cell therapies** have been approved by FDA to **treat multiple cancer types**.	

GENETIC AND EPIGENETIC CONTROL OF CELL FUNCTION

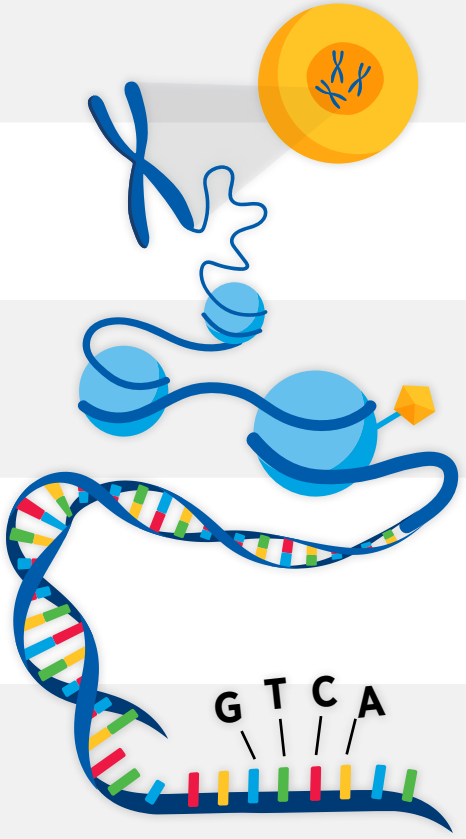
The genetic material of a cell comprises strings of **deoxyribonucleic acid (DNA)**, a complex molecule comprised of four units called bases.

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**.

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 (129).

Alterations in the DNA sequence, referred to as mutations, can disrupt normal protein function, and are the leading cause of cancer development (see sidebar on **Genetic Mutations**, p. 30). Each person's cancer has a unique combination of mutations, and as cancer cells divide, new mutations arise in the daughter cells. Thus, a tumor is made up of a collection of cancer cells with a wide range of genetic abnormalities. This variation in cell types, also known as tumor heterogeneity, is evident in most tumors. Tumor heterogeneity fuels the cancer's ability to grow faster and metastasize, escape therapy, and evade destruction by the immune system. Therefore, characterization of tumor heterogeneity is an area of extensive research investigation (130,131).

While inherited genetic mutations, often associated with cancer predisposing syndromes, play a role in about 10 percent of all cancer cases (see **Table 2**, p. 31), most mutations are acquired over an individual's lifetime due to errors arising during normal cell multiplication or because of environmental exposures, lifestyle factors, or coexisting health conditions (see sidebar on **Sources of Genetic Mutations**, p. 32). Ongoing

THE HONORABLE
Bennie Thompson

U.S. Representative for Mississippi's 2nd District

"The National Cancer Act changed the lives of Mississippians, and the lives of those struggling with cancer across the nation. Cancer research has played a vital role in helping Members of Congress craft legislation to assist those who are suffering. As a Member of Congress, and a Representative of the State of Mississippi, I will remain a staunch supporter of legislation that advances and assists those whose lives are impacted by cancer."

GENETIC MUTATIONS

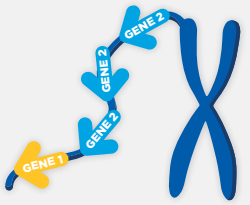
Types of genetic mutation known to lead to cancer include:

Single base changes

- Deletion, insertion, or substitution of a single base can result in new proteins, altered versions of normal proteins, or loss of protein function, which can lead to cancer.

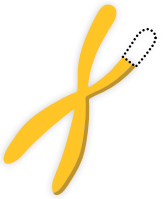
Extra copies of genes (gene amplification)

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



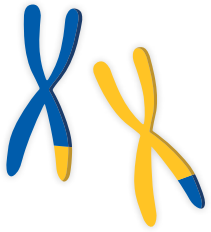
Deletions

- 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.



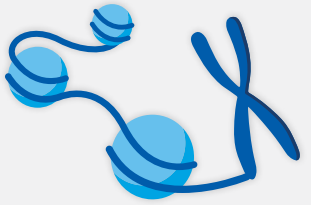
Structural variations

- 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.



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 the genes that produce these proteins can lead to cancer by altering the coordinated 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 (129).

research continues to uncover the mutational landscape of specific cancer types providing new insights into the genetic basis of cancer (130,132,133) (see sidebar on **Unraveling the Complexities of Cancer Genomics**, p. 33).

Not all mutations acquired by a cell lead to cancer. In fact, the genes that are mutated, and the order and speed at which a cell acquires mutations, determine whether a cancer will develop and, if a cancer does develop, the length of time it will take to happen. The progressive nature of cancer provides distinct time points for medical intervention to prevent, detect, and/or intercept cancer early, and to treat progressive disease (149). In general, the further a cancer has progressed, the harder it is to stop the chain of events that leads to the emergence of metastatic disease, which is the cause of most deaths from solid tumors. Therefore, understanding the cellular and molecular events that contribute to the transition from healthy to precancerous cells to progressive disease is an area of immense scientific focus (150–152).

In addition to genetic mutations, changes in the physical structure of DNA caused by chemical modifications of the DNA and/or the proteins associated with it, termed epigenetic modifications, can lead to cancer development (see sidebar on **Genetic and Epigenetic Control of Cell Function**, p. 29). Epigenetic modifications regulate how and when our genes are turned "on" or "off," and they are made by specialized proteins that "add" or "erase" unique chemical modifications of DNA and/or histones (153). In contrast to genetic mutations, epigenetic changes are often reversible,

TABLE 2

INHERITED CANCER RISK

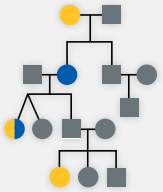
Cancers	Syndrome	Associated Gene(s)
Leukemias and lymphomas	Ataxia telangiectasia	*ATM*
Basal cell carcinoma and medulloblastoma	Basal cell nevus syndrome	*PTCH1, PTCH2, SUFU*
All cancers	Bloom syndrome	*BLM*
Breast, ovarian, pancreatic, and prostate cancers	Breast-ovarian cancer syndrome	*BRCA1, BRCA2*
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

SOURCES OF GENETIC MUTATIONS

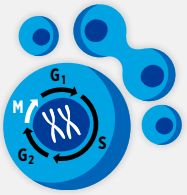
Cancer initiation and progression are predominantly caused by the accumulation of changes, or mutations, in the genetic material of a cell over time. The primary sources of genetic mutations are as follows:

Nearly 10 percent of cancer cases are linked to inherited genetic mutations (see **Table 2**, p. 31), which are mutations that are present in each cell of the body from birth (134–137).

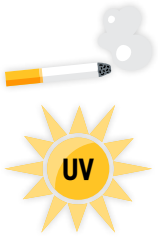


Most mutations, however, are acquired during a person's lifetime.

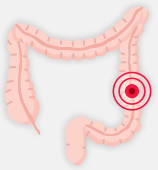
Some occur during cell multiplication, and the number of times a cell multiplies increases the chance that it will acquire a mutation.



Some occur because of persistent exposure to substances that damage genetic material, such as carcinogens in tobacco smoke and ultraviolet radiation from the sun (see **Figure 7**, p. 37).



Other mutations occur because of chronic inflammation caused by medical conditions such as Crohn's disease (135,138).



These factors come together to determine the chance that an individual cell has of acquiring mutations over time, which in turn determines the overall risk that a person will develop cancer. It is important to note that not all mutations lead to cancer.

Adapted from (139).

providing an opportunity for therapeutic intervention. Our understanding of the role of epigenetics in cancer is continuously evolving, and ongoing research is uncovering the enormous potential of targeting epigenetic pathways in cancer treatment (154,155).

Research aimed at the identification of genetic and epigenetic alterations that drive cancer development has led to the development of a new class of treatments—molecularly targeted therapeutics—which aim to rectify the cellular changes that arise due to such alterations. While these advances have revolutionized clinical cancer care for some patients, they have also brought attention to the fact that racial or ethnic minorities are grossly underrepresented in genetic databases and in most clinical research investigations, including those in cancer science and medicine (156,157). The lack of diversity in cancer genomic studies limits our understanding of cancer biology, including inherited cancer predisposition, in underrepresented populations. Rectifying this issue is an area of active research investigation, as reported in the *AACR Cancer Disparities Progress Report 2020* (91).

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.

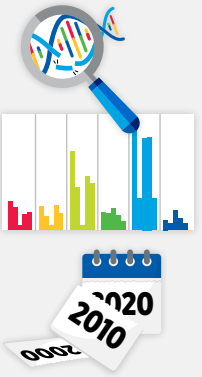
The tumor microenvironment is a specialized niche surrounding the cancer cells in a tumor and consists of immune cells—components of one's natural defense mechanism—as well as other cellular and molecular elements (see sidebar on **Cancer Growth: Local and Systemic Influences**, p. 34). Bidirectional communications between cancer cells and their microenvironment affect tumor progression and metastasis (158–160). The tumor microenvironment can also shelter cancer cells from the effects of radiation, chemotherapy, and immunotherapy, thereby rendering them resistant to treatment (161,162).

Ongoing research is likely to uncover additional mechanisms by which the tumor microenvironment interacts with cancer cells which may, in turn, lead to the development of new and improved treatments against cancer. For instance, two new studies unraveled key cellular and molecular features of the tumor microenvironment that are critical for keeping tumors in check and may be utilized for future therapeutic targeting of aggressive cancers such as pancreatic cancer and melanoma (163,164). Yet another series of recent articles characterized lung cancer cells and their microenvironment (165,166). The data provide deep insights into the interactions between the immune microenvironment and cancer cells in different regions within a tumor and across different tumors in a patient (167,168). The studies further characterize the wide range of alterations, including mutations, within immune and cancer cells that enable

UNRAVELING THE COMPLEXITIES OF CANCER GENOMICS

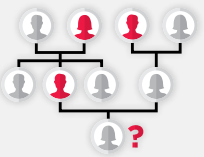
Recent work from an international team of scientists has provided critical insights into cancer genomics with potential implications for early detection, interception, and treatment. The researchers analyzed the whole genome from >2,600 tumor samples spanning 38 different types of cancer (140). Among the most important findings were the following:

- Most tumors contain at least **one identifiable mutation in their genomes that appears to drive tumor growth**, and on an average each cancer genome was found to contain between four and five such "driver" mutations (141).
- Unique patterns of mutations referred to as **"mutational signatures" are often associated with processes or events that may lead to cancer development**, such as defective DNA repair mechanisms or exposure to cancer risk factors such as environmental carcinogens, toxicants in tobacco smoke, or ultraviolet radiation (142).
- By analyzing the vast array of genetic changes, the researchers were able to determine the chronology of cancer-causing mutations. They found that **many mutations can occur years, if not decades, prior to a cancer diagnosis** (143).



Results from three recent studies have provided a **deeper understanding of the inherited genetic mutations that predispose women to breast cancer**, the prevalence of such mutations in the general population, and the earliest cellular and molecular changes in presumably healthy breast tissue, prior to tumor development, among individuals with inherited mutations (144–146). These data are critical for the development of early diagnostic testing or cancer prevention interventions for women who are susceptible to breast cancer development.

In a recent paper, researchers outlined new details regarding the **contribution of inherited genetic mutations in the development of childhood cancers** (147). These data can be used not only to select the most appropriate treatment for certain patients, but also to tailor prevention and screening for patients and/or their family members who harbor similar mutations and even for future family planning purposes.



Data from a recent publication provide significant **new insight into the development of blood cancers** (148). Notably, the study reported that certain mutations associated with leukemia or other blood cancers are also detected, albeit at low levels, among seemingly healthy individuals, showcasing a potential for precancer surveillance and/or interception.

lung cancers to evade attack and elimination by the immune system (169–171). Collectively, these discoveries have critical implications in understanding cancer progression and relapse, as well as a tumor's response to state-of-the-art treatments such as immunotherapies.

Cancer Development: Integrating Our Knowledge

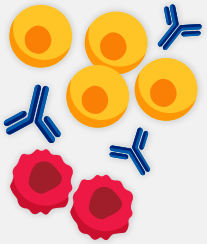
The remarkable progress in discovery science during the past five decades has transformed our understanding of the complex group of diseases we call cancer. We have learned that cancer development is influenced by many factors, including a patient's biological characteristics, social and environmental exposures, and lifestyle. As each person's experience is unique, so is his or her cancer. As a result, we are beginning to see a major shift from a "one size fits all" paradigm to cancer prevention, screening, and treatment to a more personalized approach called precision medicine (see **Figure 6**, p. 35).

Notably, we have also learned that even among patients with the same type of cancer based on traditional classification, each patient's response to treatment is unique. For example, a recent analysis of the cellular and molecular characteristics of tumors derived from patients with metastatic cancers showed that the response to the same treatment can vary widely among patients. In fact, the researchers were able to

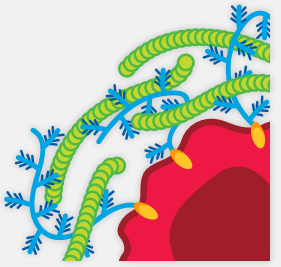
CANCER GROWTH: LOCAL AND SYSTEMIC INFLUENCES

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

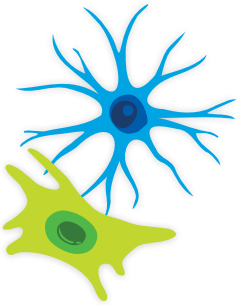
Immune cells can identify and eliminate cancer cells, although in many cases the immune system is suppressed, permitting the formation and progression of a tumor. However, in some situations of chronic inflammation, the immune system can promote cancer development and progression.



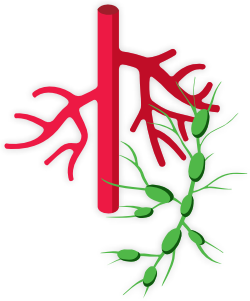
The **matrix of proteins** that surrounds the cancer cells can influence cancer formation and metastasis.



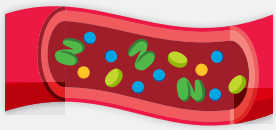
Other tissue-specific **tumor-associated cells**, such as pericytes, fibroblasts, and astrocytes, can support tumor growth through various mechanisms including stimulating tumor cell multiplication, triggering formation of new blood vessels, and enhancing survival of cancer cells.



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).



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



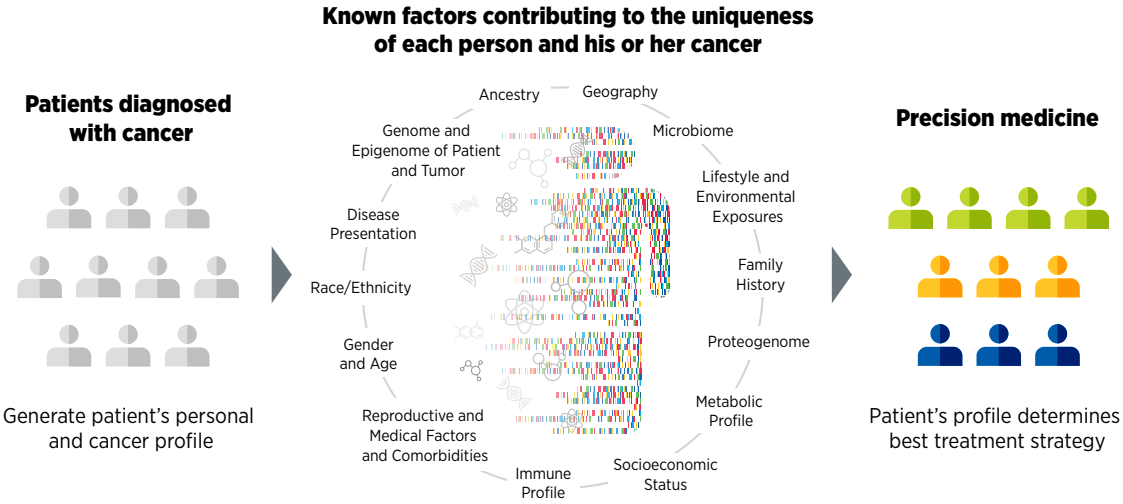
Adapted from (172).

identify a subset of patients who responded exceptionally well to therapeutics that are usually only effective in fewer than 10 percent of individuals with similar cancer types (173). The researchers further identified patterns within tumor cells and the microenvironment that could potentially explain the exceptional responses to treatment. Knowledge gained from studies such as these, and other ongoing and future investigations that characterize the genetic and epigenetic alterations within tumors and the microenvironment will help us move closer to the promise of delivering precision medicine for all patients with cancer.

Precision medicine aims to use genetic and other information about a patient's tumor, as well as other factors, to 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, tumor genetics is the predominant factor guiding precision medicine in cancer, and there are emerging data that the adoption of this approach provides substantial survival benefits for patients (174–176). Ongoing efforts are focused on identifying innovative approaches, such as new tools that harness genetic information to predict patients' responses to cancer treatments, to maximize the number of patients who can benefit from precision medicine (177). Researchers are also pursuing novel avenues beyond tumor genetics, e.g., protein composition of tumor cells, microbial composition in the gut, and restrictive or altered diets, among others, to boost the power of precision medicine for cancer patients (178,179). Integration of data collected through such multipronged approaches will provide

FIGURE 6

PRECISION MEDICINE



Precision medicine is broadly defined as treating patients based on characteristics that distinguish them from other individuals with the same disease. As shown in the figure, the factors that contribute to the uniqueness of a patient and his or her cancer include, but are not limited to, the person's genome, the genome and epigenome of his or her cancer, the immune characteristics of the person and his or her cancer, disease presentation, gender, ancestry, exposures, lifestyle, microbiome, and comorbidities.

Currently, genomics is the predominant factor influencing precision medicine, but as we learn more about the additional factors, such as epigenomics, proteogenomics, and tumor immune characteristics, we will be able to create an even more personalized approach to cancer treatment. It is important to note, however, that the cost effectiveness of such profiling still needs to be evaluated alongside ongoing efforts to define which and to what extent profiling improves outcomes for individuals.

further insights into cancer diagnosis and treatment, opening new opportunities in precision medicine. Yet another area of active focus is the accumulation of relevant data from racial and ethnic minorities, the lack of which substantially minimizes the current implementation of precision medicine for these populations (91). Going forward, concerted efforts from all stakeholders in medical research and public health will be critical to ensure that every cancer patient in the United States benefits from the promise of precision medicine.

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, but more than 41 percent of U.S. adolescents have not yet received the recommended doses of the vaccine.
- The mechanisms by which certain risk factors such as obesity, unhealthy diet, and physical inactivity increase cancer incidence are currently under investigation.

Factors that increase a person's chances of developing cancer are referred to as cancer risk factors. Decades of research have led to the identification of numerous cancer risk factors (see **Figure 7**, p. 37) such as tobacco use, poor diet, physical inactivity, obesity, infection with certain pathogens, and exposure to ultraviolet (UV) radiation. Given that several of these risks can be avoided, many cases of cancer could potentially be prevented. In fact, according to a recent report, healthy lifestyle habits can reduce risks even among those with a higher genetic risk for cancer (see sidebar on **How Do I Know If I Am at High Risk for Developing an Inherited Cancer?**, p. 66) (180). In the United States, more than 40 percent of all new cancer cases diagnosed in 2014, which are the most recent data available, were attributable to preventable risk factors (181). Emerging data indicate that certain cancer risk factors are also associated with worse outcomes after a cancer diagnosis including development of secondary cancers (182,183).

Many cancer risk factors also contribute to other chronic diseases, such as cardiovascular disease, respiratory diseases, and diabetes. Therefore, reducing or eliminating exposure through lifestyle changes, behavior modifications, public education, and policy implementation has the potential to reduce the burden of cancer as well as several other diseases.

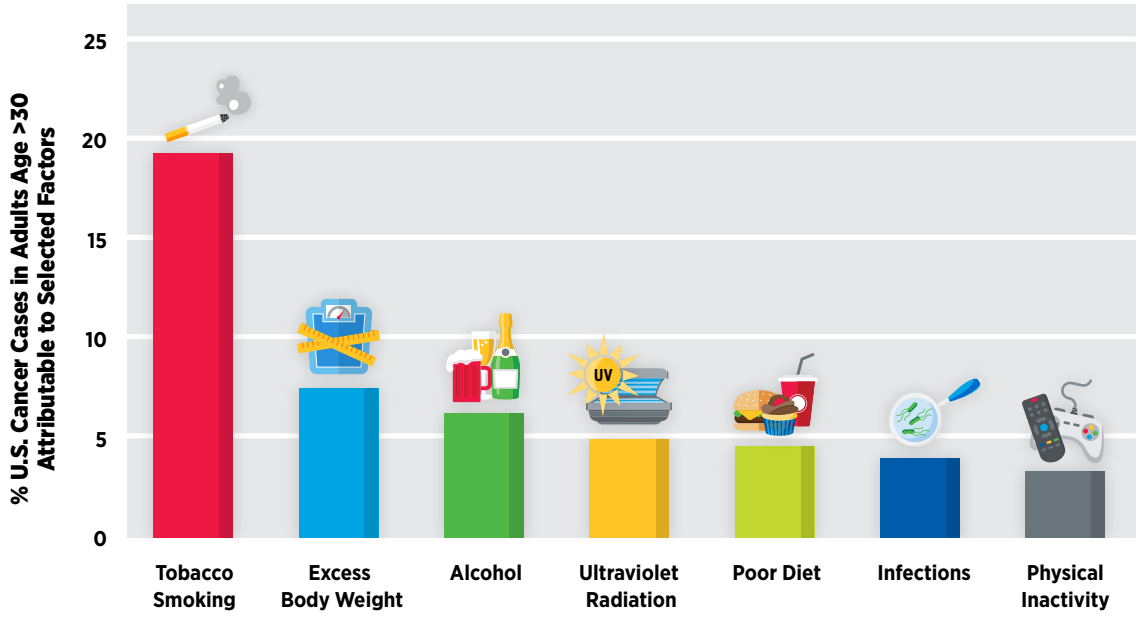
In the United States, many of the greatest reductions in cancer morbidity and mortality have been achieved through the implementation of effective public education and policy initiatives. For example, such initiatives have helped reduce cigarette smoking rates among U.S. adults by 67 percent from 1965 to 2019 (23). These reductions have contributed significantly to the dramatic decline in overall U.S. cancer mortality rates (3). However, cigarette smoking still accounted for nearly four out of 10 cancer deaths in parts of the United States between 2013 and 2017 (185). It is also concerning that the prevalence of certain cancer risk factors, such as obesity has been rising steadily among U.S. adults (186–188). Consequently, progress in terms of mortality reduction has slowed down for obesity-related cancers compared to cancers not associated with obesity (189). There are, however, significant disparities in the burden of cancer risk factors among certain segments of the U.S. population such as racial and ethnic minorities and individuals from low socioeconomic status (see sidebar on **Disparities in the Prevalence of Preventable Cancer Risk Factors**, p. 38). Therefore, it is imperative that all stakeholders come together to identify better strategies for the dissemination of our current knowledge of cancer prevention and implementation of effective evidence-based practices that promote a healthier lifestyle among all populations.

Eliminate Tobacco Use

Use of tobacco is the leading cause of preventable disease, disability, and death in the United States, taking more than 480,000 lives each year (196). Smoking tobacco has been shown to increase the risk of developing 17 different types of cancer in addition to lung cancer (see **Figure 8**, p. 39). Smokers are exposed to numerous harmful chemicals that damage DNA, causing genetic and epigenetic alterations that lead to cancer development (197–199). Fortunately, quitting tobacco at any age can reduce risks from cancer as well as several other smoking-related adverse health effects, such as cardiovascular and pulmonary diseases (200).

FIGURE 7

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.

Figure adapted from (184).

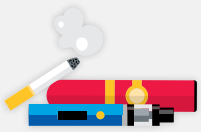
Thanks to the implementation of nationwide comprehensive tobacco control initiatives, cigarette smoking among U.S. adults has been declining steadily (201). In 2019, which is the most recent year for which such data are available, 14 percent of U.S. adults age 18 and older smoked cigarettes, a significant decline from 42.4 percent of adults in 1965 (23,201). Cigarette use has also declined among U.S. youth, especially over the past decade (21). However, nearly 51 million adults and 4.5 million middle and high school students in the United States were still using some type of tobacco product in 2019 and 2020, respectively (23,202). It has been documented that most adult users initiate smoking in their youth. Recent studies corroborate these findings further showing that among youth who were previously nonsusceptible to cigarette use, many initiate smoking between ages 16 and 18 years although the age at initiation varies by sex and race or ethnicity (203). Recent data also suggest that the age of smoking onset may be shifting upward from youth to young adulthood. According to a new report, the proportion of smokers who initiated smoking in their early adulthood, between ages 18 and 23 years, more than doubled between 2002 and 2018 (204). Collectively, these data reinforce the fact that smoking prevention efforts targeting youth and young adults are vital and may have significant, long-term positive impact on smoking-related health outcomes.

It is imperative that researchers, public health experts, and policy makers work together to identify evidence-based, population-

Globally, **1.14 billion people were current smokers in 2019.** Although prevalence of smoking has decreased significantly since 1990, smoking accounted for **7.69 million deaths in 2019 globally**, including deaths from cancer (205).

DISPARITIES IN THE PREVALENCE OF PREVENTABLE CANCER RISK FACTORS

There are considerable disparities in the exposure to avoidable cancer risk factors among certain segments of the U.S. population, such as:



The prevalence of **tobacco product use is higher** among non-Hispanic American Indian/Alaska Native adults (29.3%) and lower among non-Hispanic Asian adults (11.0%) compared to non-Hispanic white adults (23.3%) (23).

The prevalence of **secondhand smoking exposure is twice as high** among nonsmoker non-Hispanic Blacks (48.02%) compared to non-Hispanic whites (22.03%) (190).

Among youth ages 10 to 17, **obesity rates were significantly higher** for non-Hispanic Blacks (22.9%), Hispanics (20.7%), non-Hispanic American Indians/Alaska Natives (28.5%), and non-Hispanic Native Hawaiians/other Pacific Islanders (39.8%) compared to non-Hispanic whites (11.7%) and non-Hispanic Asians (5.9%) (191).

In Philadelphia, PA, **neighborhoods with the lowest median income** have 28% fewer stores with healthier foods per capita compared to places with the highest median income; more people living in areas with an overabundance of unhealthy food are Black (45%) compared to white (27%) (192).

The prevalence of physical inactivity is higher among people with less than a high school education (48.2%) compared to those who are college graduates (14.5%) (193).

The **rate of acute hepatitis C infection is higher** (3.6 cases per 100,000 population) among American Indians/Alaska Natives and lower (0.2 cases per 100,000 population) among Asians/Pacific Islanders compared to non-Hispanic whites (1.4 cases per 100,000 population) (194).

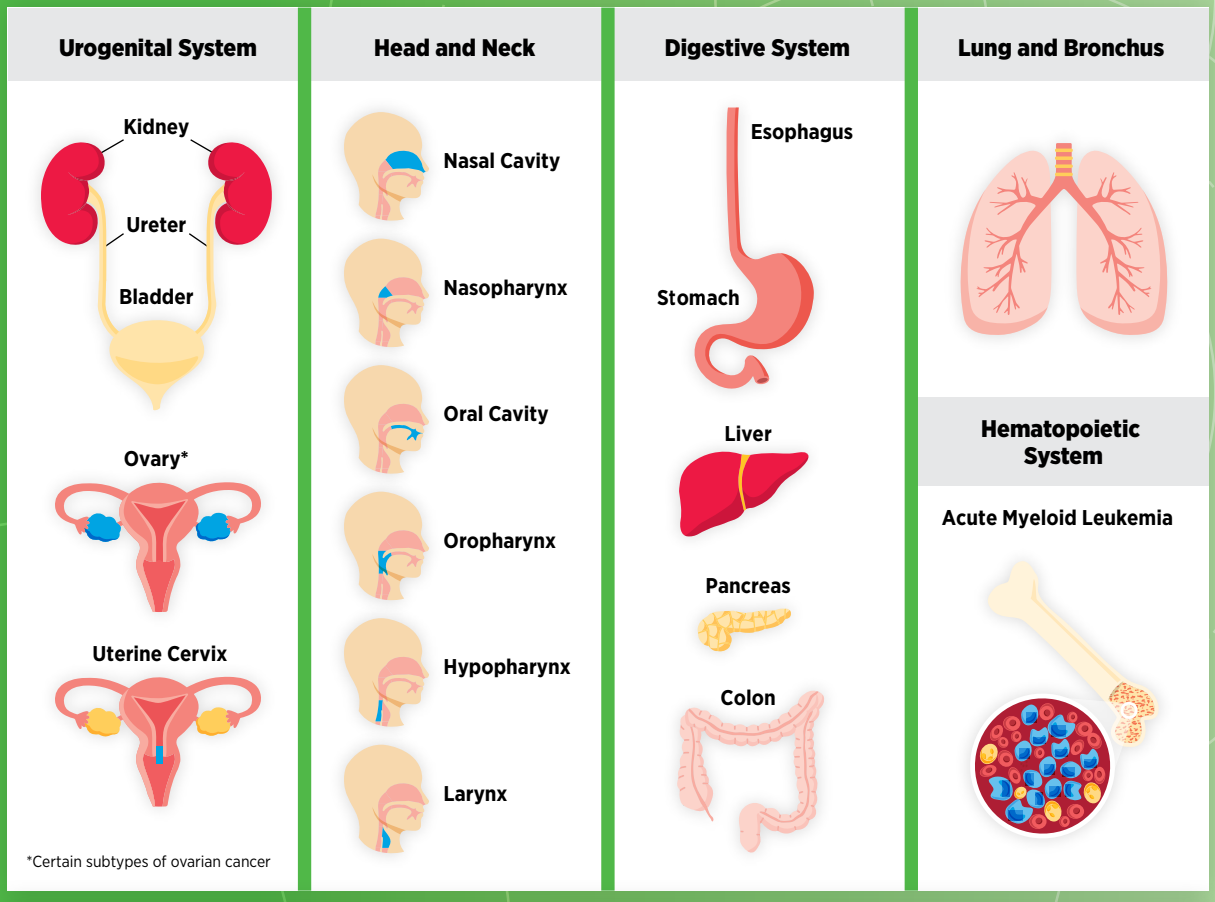
Racial and ethnic minorities are **60 percent more likely to live in a U.S. county with unhealthy levels of air pollution** compared to whites (195).

level interventions such as tobacco price increases, public health campaigns, age and marketing restrictions, cessation counseling and medications, and smoke-free laws to further reduce smoking rates and smoking-related cancer burden in the United States. Effective interventions should also help drive down secondhand smoke exposure which is a risk factor for lung cancer among adult nonsmokers. Recent reports indicate that innovative interventions such as smoking cessation advice along with free samples of nicotine replacement therapy offered to expectant fathers or a smartphone application-based therapy offered to parents while they are visiting the office of their child's pediatrician can increase smoking cessation (206–208). Ongoing research in this area is essential, since over half of adult smokers try to quit smoking each year but fewer than 10 percent are successful (200). Notably, FDA-approved therapeutics and behavioral counseling have both been shown to improve the chances of quitting smoking and using them together can double the odds of quitting successfully (200).

The use of other combustible tobacco products (for example, cigars), smokeless tobacco products (for example, chewing

FIGURE 8

BEYOND THE LUNGS: CANCERS CAUSED BY SMOKING TOBACCO



Smoking tobacco increases an individual's risk of developing not only lung cancer, but also 17 other types of cancer. No level of exposure to tobacco smoke is safe, including exposure to secondhand smoke, which is estimated to have resulted in more than 260,000 of the 5 million lung cancer deaths in the United States attributable to smoking from 1965 to 2014.

Figure adapted from (129).

- According to U.S. Preventive Services Task Force (USPSTF), **behavioral interventions and/or FDA–approved therapeutics** for nonpregnant adults and **behavioral interventions** for pregnant adults are **effective in increasing smoking cessation** (209).
- **USPSTF recommends that clinicians ask all adults about tobacco use**, advise them to stop using tobacco, and provide behavioral interventions and/or FDA-approved therapeutics to nonpregnant smokers or behavioral interventions to pregnant smokers for cessation (210).

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 (214).

Constituents and users' exposure to toxicants

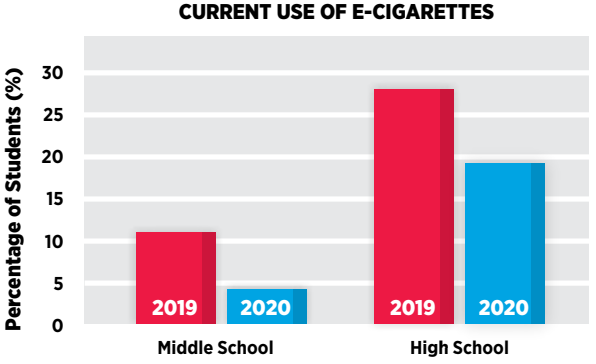
- E-cigarettes can deliver as much nicotine as a pack of cigarettes.
- Completely switching to e-cigarettes from regular use of conventional cigarettes can reduce exposure to toxic chemicals. However, it should be noted that e-cigarettes are not harmless; in addition to nicotine, e-cigarettes contain and emit numerous potentially toxic substances including heavy metals, volatile organic compounds, tobacco-specific nitrosamines, aldehydes, phenolic compounds, and polycyclic aromatic hydrocarbons (214).

Role in smoking cessation and initiation

- More research is needed to evaluate their value as smoking cessation aids.
- Use increases the probability of youth or young adults transitioning to conventional cigarettes (217); according to a recent report, e-cigarette use among youth increased the risk of later daily cigarette smoking by threefold (218).

Use

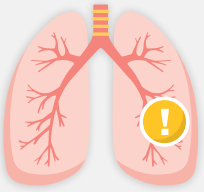
- Use is highest among youth and young adults and most young users prefer flavored e-cigarettes such as fruit, menthol, and mint (215).
- Use among middle and high school students rose at an alarming rate between 2011 and 2019; while it is encouraging that between 2019 and 2020 use has declined in both populations, public health professionals are now concerned about the recent increase in popularity of disposable devices (216).



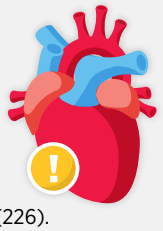
Human health effects

Immediate health hazards

- Intentional or accidental exposure to e-liquid (from drinking or other contact) can have serious adverse health effects.
- E-cigarettes can explode causing burns and other injuries.
- There have been cases of seizures following e-cigarette use, mostly in youth and young adults (219).
- Vitamin E acetate, an additive in some tetrahydrocannabinol (THC)-containing e-cigarettes, can cause serious lung injuries (220-225). THC is the primary psychoactive ingredient in marijuana.



Long-term adverse effects



- There are indications that vaping can pose significant risks to vascular and respiratory health (226–228). Even former users are at a 28 percent higher risk for respiratory diseases compared to never users, according to a new study (226).
- Preliminary data indicate that several carcinogens known to be linked to bladder cancer are present in the urine of e-cigarette users (229).
- 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.

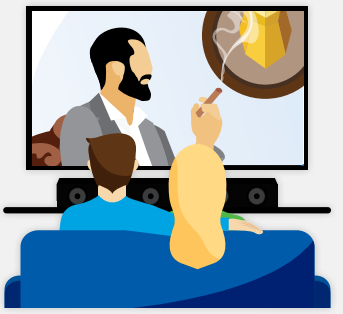
Adapted from (184).

tobacco and snuff), and waterpipes (hookahs) is also associated with adverse health outcomes including cancer (211). Electronic cigarettes (e-cigarettes) have gained enormous popularity among U.S. youth and young adults over the past decade (see sidebar on **E-Cigarettes: What Have We Learned and What Do We Need to Know?**, p. 40). E-cigarettes, first introduced to the U.S. market in 2007, have been the most used tobacco product among U.S. middle and high school students since 2014 (202,212). Since their introduction to the U.S. marketplace, the landscape of e-cigarettes has evolved to include different types of products such as prefilled pods (cartridge–based devices), and disposable (single use) devices, among others. E-cigarettes come in flavors that appeal to youth, and these flavors are key drivers of use among youth and young adults. E-cigarettes deliver very high levels of nicotine, an extremely addictive substance, that is harmful to the developing brain (213), and are known to contain high levels of other toxic chemicals including reactive aldehydes (214).

The surge in the use of e-cigarettes between 2011 and 2019 among youth and young adults, populations especially vulnerable to the detrimental effects of nicotine, raised great concern among U.S. public health officials. In December 2018, the Office of the U.S. Surgeon General issued an advisory declaring e-cigarette use in youth an epidemic, and since then FDA, the federal government, and many local governments have proposed several restrictions on e-cigarettes including bans on certain flavors to curb youth appeal (see **Reducing Tobacco-related Illness Through Public Health Policy**, p. 148). Therefore, it is encouraging that the use of e-cigarettes declined among U.S. youth and young adults between 2019 and 2020. However, 3.6 million youth and young adults still reported using e-cigarettes in 2020 (216). Clearly, more work needs to be done to effectively curb the use of these products. Beyond the United States, e-cigarettes are emerging as a serious public health threat globally, necessitating the WHO to call for better regulation of these products in its latest report on the global tobacco epidemic (230).

It is known that more than 80 percent of e-cigarette users prefer flavored products. In February 2020, FDA implemented certain restrictions on flavoring in pod/cartridge-based e-cigarettes (see **Reducing Tobacco-related Illness Through Public Health Policy**, p. 148). While these are welcome changes, one outstanding concern is that disposable products were exempted from any flavor restrictions, leaving many youth-friendly flavors on the market. Notably, there has been a striking surge in the use of disposable products among middle (400 percent) and high school (1000 percent) students between 2019 and 2020 (216). Recent data also suggest that many youth and young adults were able to access e-cigarettes from online stores (instead of regular retail shops) during the COVID-19 pandemic, emphasizing the need for strict enforcement of policies such as age verification to limit youth access (231).

Interestingly, based on a new survey that polled 498 e-cigarette users between ages 12 and 17 years, nearly half of the participants expressed interest in quitting, highlighting the vital need for evidence-based e-cigarette cessation interventions (232). In this regard, a recent clinical trial conducted among e-cigarette users between ages 18 and 24 showed that a text message-based cessation intervention that delivered social support and cognitive and behavioral coping skills to the participants was effective at helping more than 24 percent of participants abstain from e-cigarettes for up to seven months of follow-up (233). Whether similar interventions have the potential to be effective among younger users remains to be assessed.



Exposure to tobacco content in programs on Netflix and broadcast or cable TV is associated with significantly higher odds of initiating e-cigarette use among youth and young adults (234).

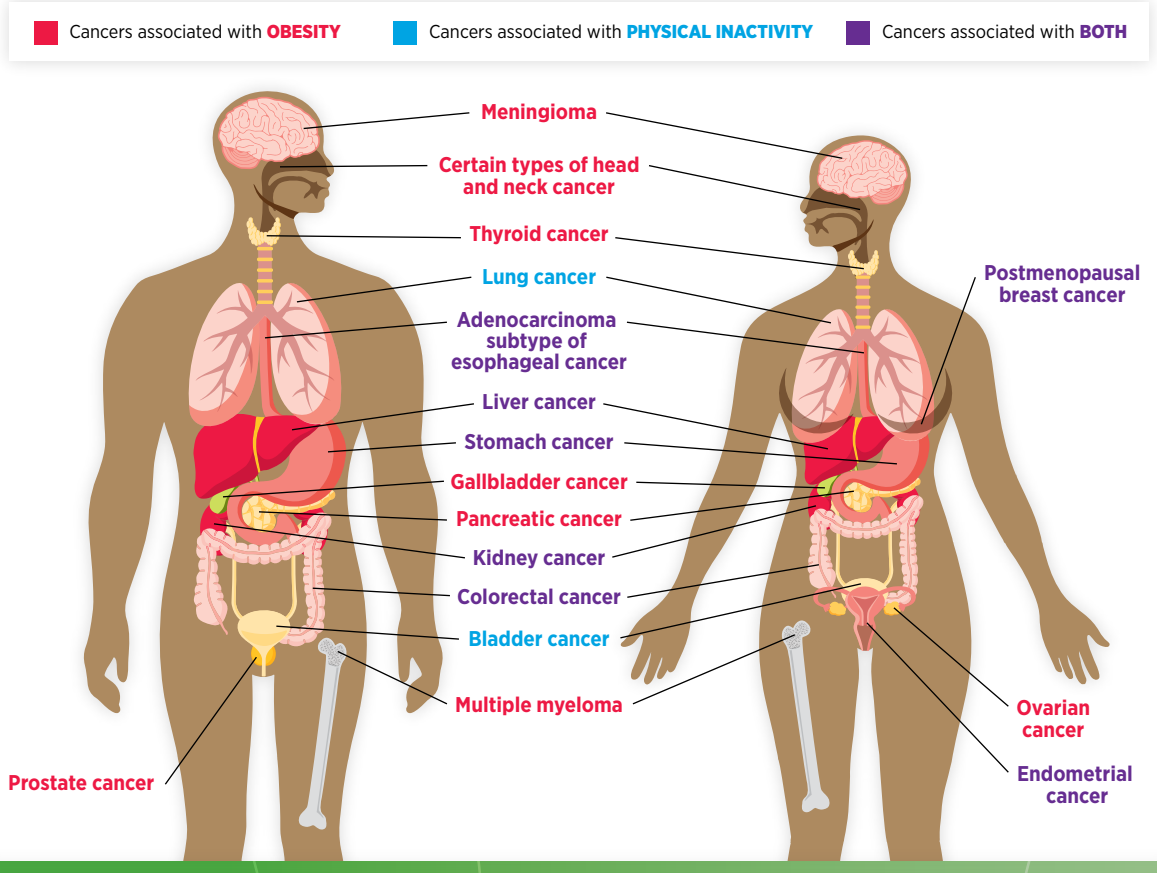
While the prevalence of e-cigarette use in U.S. adults is lower than that in youth and young adults, it must be noted that nearly 80 percent of adult e-cigarette users are either current or former smokers, and most users report using or having used e-cigarettes to quit smoking (235) even though there is no clear evidence that e-cigarettes are effective as a smoking cessation tool. There are, however, data that former smokers who use e-cigarettes are more likely to experience a smoking relapse (236). In addition, there are accumulating data on the adverse health outcomes of e-cigarette use. For instance, according to a new study from a nationally representative cohort of U.S. adults, e-cigarette use was shown to be associated with a significantly increased risk of major respiratory diseases, such as COPD, emphysema, and asthma independent of the use of cigarettes or other types of tobacco products (226). Clearly, the significant harm to public health outweighs the currently unclear role in smoking cessation among adult smokers. It is imperative that public health professionals continue to evaluate the long-term health outcomes associated with e-cigarette use and gather definitive evidence on their role in smoking cessation.

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

FIGURE 9

REASONS TO MAINTAIN A HEALTHY WEIGHT AND STAY ACTIVE



Fifteen types of cancer—the adenocarcinoma subtype of esophageal cancer; certain types of head and neck cancer; advanced prostate cancer; meningioma; 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 purple.

Data from (237-243). Figure adapted from (139).

of excess body weight, poor diet, physical inactivity, and alcohol consumption (181). Being overweight or obese as an adult increases a person's risk for 15 types of cancer; being physically active reduces risk for nine types of cancer (see **Figure 9**). 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 **Reduce Your Risk for Cancer by Maintaining a Healthy Weight, Being Physically Active, and Consuming a Balanced Diet**, p. 43). 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.

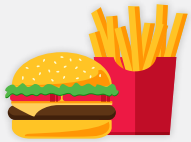
The prevalence of obesity has been rising steadily in the United States. In 2018, which is the most recent year for which data are available, 21 percent of youth ages 12 to 19, and 42 percent of adults age 20 and older were considered obese (186,244). There are, however, stark disparities based on levels of income as well as race/ethnicity (186). It is also

REDUCE YOUR RISK FOR CANCER BY MAINTAINING A HEALTHY WEIGHT, BEING PHYSICALLY ACTIVE, AND CONSUMING A BALANCED DIET

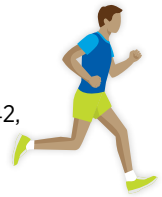
Research shows that about one-fifth of all cancers diagnosed in the United States can be attributed to being overweight or obese, being physically inactive, eating poorly, and drinking excessively. Based on current evidence, experts from the World Cancer Research Fund International recommend people (252):

Maintain a healthy weight because 15 types of cancer have been causally linked to being obese or overweight (see **Figure 9**, p. 42).*

Limit consumption of "fast foods" and other processed foods high in fat, starches, or sugars because these contribute to weight gain.

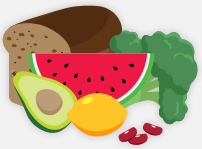


Be physically active as part of everyday life; regular physical activity can decrease risk for nine types of cancer (see **Figure 9**, p. 42, and sidebar on **Physical Activity Guidelines**, p. 45).



Limit intake of red and processed meats (e.g., hot dogs, bacon, and salami) because these foods can increase risk for colorectal cancer.

Eat a diet rich in vegetables, fruits, whole grains, and beans because these foods have a low energy density and, therefore, promote healthy weight.



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

For mothers, **breastfeed** baby, if able.

If consumed at all, **limit alcoholic drinks**, because alcohol consumption can increase risk for six types of cancer (see **Figure 10**, p. 46).

*Overweight and obesity are most often assessed using BMI: BMI between 18.5 and 24.9 is considered healthy weight.

Source: (241,252)

concerning that 40 percent of U.S. adults who are overweight and nearly 10 percent of adults who are obese do not consider themselves to be overweight (245). Notably, among individuals who are obese, awareness of their obesity status is associated with a 2.5-fold increase in their attempts to lose weight (245). Collectively, these data highlight the need for public education to raise awareness about the adverse health outcomes of excess body weight, as well as the importance of evidence-based interventions to help maintain a healthy weight. In this regard, a recent clinical trial conducted at several primary care clinics serving racially diverse low-income populations across Louisiana showed that a diet, exercise, and health coaching-based intervention resulted in significantly higher weight loss over 24 months when compared to routine primary care (246).

Over the past three decades, the United States has witnessed unprecedented progress against cancer as is evident by a steady decline in overall cancer mortality rates. Unfortunately, the rising obesity trends threaten to slow down this progress against cancer. In fact, recent data show that while the decline in mortality rates over the past two decades accelerated for cancers not associated with obesity, mortality improvements have decelerated for obesity-associated cancers (189). Beyond cancer, obesity increases the risk of developing and dying from several other health problems including type 2 diabetes, high blood pressure, stroke, and heart, liver, and kidney disease. Most recently, obesity has been shown to be associated with worse outcomes from COVID-19 (247). Encouragingly, according to a recent report, weight loss between early adulthood and midlife among individuals who were obese during their early adulthood

is associated with a greater than 50 percent reduction in the subsequent risk of early death (248). There are also emerging data showing that weight loss intervention through bariatric surgery may lower the future risk of certain obesity-related cancers (249–251). While further research is needed to elucidate whether weight loss can effectively mitigate risks of developing and/or dying from all obesity-related cancers, evidence-based population-level interventions to address obesity must certainly be a top priority among U.S. public health efforts.

Complex and interrelated factors ranging from socioeconomic, environmental, and biological to individual lifestyle factors 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 (186). To achieve and maintain good health, U.S. Department of Agriculture (USDA) and U.S. Department of Health and Human Services, in *Dietary Guidelines for Americans, 2020-2025*, recommend that individuals follow a healthy dietary pattern at every stage of life (253). 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 (253).

In the United States, more than 5 percent of all newly diagnosed cancer cases among adults are attributable to eating a poor diet (254) and there is increasing evidence linking diet to cancer incidence and outcomes. For instance, a recent analysis showed that daily intake of five servings of fruit and vegetables was associated with a 10 percent reduction of overall cancer mortality when compared to intake of two servings per day (255). There is also convincing evidence that higher intake of red meat is associated with increased risk, whereas higher intake of dietary fiber is associated with reduced risk of colorectal cancer incidence (256,257). Therefore, it is concerning that only seven percent of high school students met their fruit intake recommendations and only two percent of high school students met their vegetable intake recommendations in 2017; only 26 percent of adults met their fruit intake recommendations and 12 percent of adults met their vegetable intake recommendations in 2019 (193,258). Furthermore, individuals who are overweight or obese are even less likely to follow recommended guidelines on dietary intake (259). Intensive efforts by all stakeholders are needed if we are to increase the number of people who consume a balanced diet such as that recommended by the *Dietary Guidelines for Americans, 2020-2025*.

One of the major barriers to a healthy diet is "food insecurity," which is defined by the 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 (186). It is therefore extremely concerning that the prevalence of food insecurity increased from approximately nine percent to 18 percent between 2000 and 2016, and that racial and ethnic minorities and individuals living in poverty have significantly higher odds of living with food insecurity (260). The COVID-19 pandemic has exacerbated these challenges with indications that point to an increased level of food insecurity in 2020 compared to the previous year (186). It is imperative that all sectors work together to identify evidence-based public policies and programs that can eliminate food insecurity and ensure sustained availability of healthy food options for all Americans.

Evidence-based public policies implemented by state and federal governments play an important role in promoting healthy dietary habits. FDA, for example, recently began requiring food manufacturers to display updated nutrition labels on their product packaging. These labels must include information on added sugars and display calories and serving sizes in bolder and larger type (261). Another public policy aimed at reducing obesity is the introduction of taxes on sugar-sweetened beverages (SSBs) in several local jurisdictions in the United States (262). SSBs are a major contributor to caloric intake among U.S. youth and adults, and there are some emerging data indicating that consumption of SSBs may be associated with an increased risk of cancer incidence and mortality (263–268). Thus, it is encouraging that the prevalence of heavy SSB intake (consumption of more than 500 kcal from SSBs per day) has declined among U.S. children and adults in recent years (269). Interestingly, researchers estimate that both policies—nutrition facts/added-sugar labeling and SSB taxes—can be cost effective and can potentially result in significant health gains as well as economic benefits for all populations including those who experience cancer health disparities (270,271). Continued research is necessary to identify effective policies related to food and nutrition that maximize health

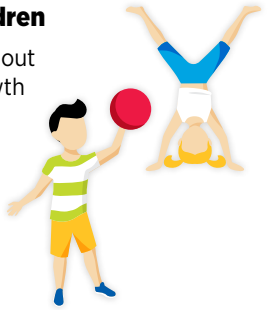
- Globally, **7.2% of all deaths are attributable to physical inactivity** (275).
- The proportion of cancers attributable to physical inactivity ranges from **~3 percent for breast or colon cancers to 7% for stomach or kidney cancers**, respectively (275).
- Because of the serious adverse health outcomes associated with sedentary behavior, in 2020, the World Health Organization for the first time provided **guidelines on sedentary behavior and physical activity** (276).

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 (237).

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

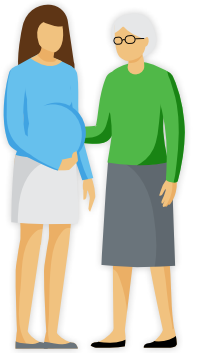
- Sixty minutes or more of physical activity (for example, running) daily
- Muscle- and bone-strengthening exercises such as push-ups at least three days per week

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 (139).

benefits and to evaluate the long-term effects of these policies on obesity and obesity-related health outcomes such as cancer.

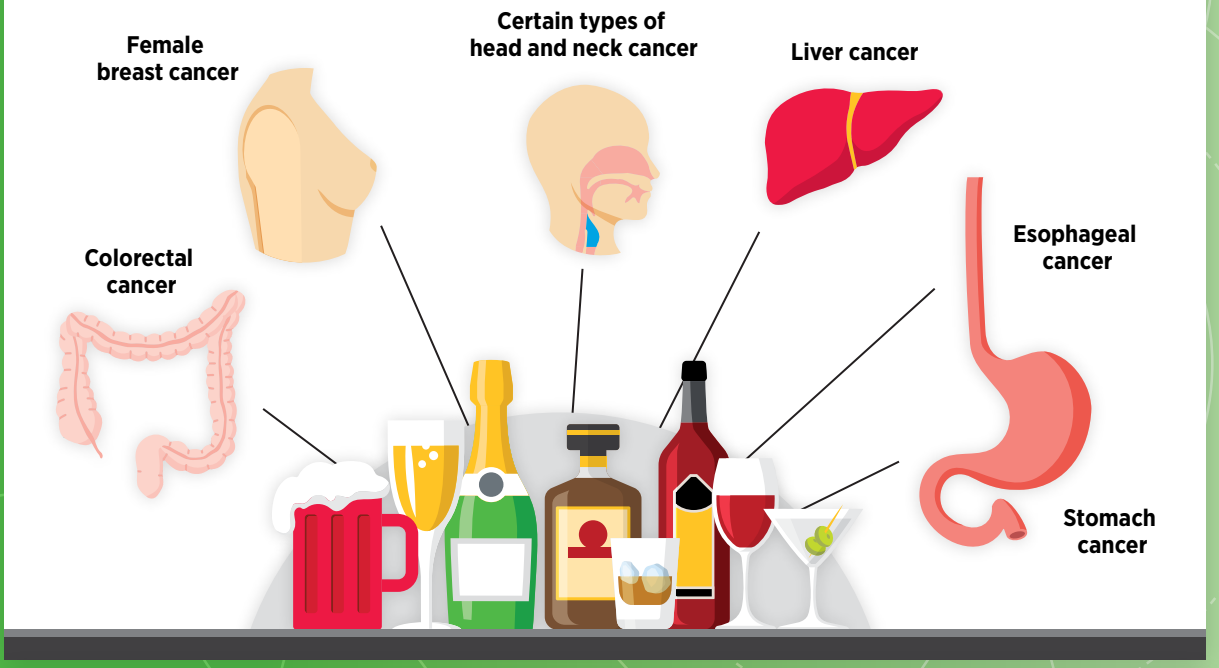
Three percent of overall cancer cases in the United States can be attributed to physical inactivity (181). According to a recent report, being sedentary (inactive) for 13 or more hours per day can increase the risk of dying from cancer by 52 percent while replacing 30 minutes of sedentary time with 30 minutes of moderate to high intensity physical activity can lower risk of cancer death by 30 percent (272). Engaging in recommended amounts of physical activity (see sidebar on **Physical Activity Guidelines**) can lower the risks for developing nine types of cancer (**Figure 9**, p. 42), and there is emerging evidence that there may be risk reduction for even more cancer types (238–240). Considering this evidence, it is concerning that more than a quarter of U.S. adults reported no leisure time physical activity in 2018, and about 17 percent of U.S. high school students reported no physical activity in 2019 (262,273). There are added concerns that the COVID-19 pandemic may have led to further decreases in physical activity and increases in sedentary behavior across several population groups (274). It is imperative that health care professionals and policy makers work together to increase awareness of the benefits of physical activity and support efforts to implement programs and policies to facilitate a physically active lifestyle for everyone.

Limit Alcohol Consumption

Drinking alcohol increases the risk for six different types of cancer (241) (see **Figure 10**, p. 46) while emerging evidence suggests that there may be risks for additional cancer types (277). Even modest use of alcohol may increase cancer risk, but the greatest risks are associated with excessive and/or long-term consumption (278–281) (see sidebar on **Guidelines for Alcohol Consumption**, p. 47). In the United States, alcohol consumption accounted for greater than 75,000 cancer cases and nearly 19,000 cancer deaths annually between 2013 and 2016 (282). In the United States, consumption of alcohol has been rising in recent years (283–285). Concurrent with increases in consumption, rates of alcohol-related deaths have also increased at an alarming rate. According to a recent report, the age-adjusted rates of all alcohol-induced deaths among adults age 25 and older increased by 43 percent between 2006 and 2018 (286). There are also concerns that the COVID-19 pandemic has further increased alcohol use in 2020 compared to previous years (287).

FIGURE 10

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.

Beyond the United States, alcohol poses a significant public health challenge globally. In fact, alcohol-use disorders are now the most prevalent of all substance-use disorders worldwide (290), and in 2020, 4.1 percent of all new cases of cancer globally were attributed to alcohol consumption (291). These data underscore the importance of adhering to comprehensive guidelines to limit alcohol intake (for those who drink) and minimize the risk of developing a disease or dying due to alcohol. Future efforts focused on public education and evidence-based policy interventions, such as regulating alcohol retail density, taxes, and prices, need to be implemented along with effective clinical strategies to reduce the burden of alcohol-related cancers. In this regard, recent studies from Canada indicate that when alcohol bottles contain labels providing drinking guidelines, as well as clear information on the risks of alcohol consumption, people are better informed about alcohol's adverse effects and may limit their drinking (292). Ongoing efforts are underway to implement similar policies requiring cancer-specific warning labels to be displayed on all alcoholic beverages in the United States (293).

Two thirds of U.S. adults age 18 and older reported consuming alcohol in 2018, and an **estimated 5.1% of adults reported heavy drinking** (289).

Protect Skin from UV Exposure

Three main types of skin cancer—basal cell carcinoma, squamous cell carcinoma, and melanoma which is the deadliest form of skin cancer—are largely caused by exposure to UV radiation from the sun or indoor tanning devices. In the United States, an estimated 91 percent of the total cases of melanoma during 2011–2015 could be attributed to UV exposure (294). Sunburn, a clear indication of excessive exposure to UV radiation, is a preventable risk factor for skin cancer, and those events occurring in childhood pose the greatest risk (295). Therefore, one of the most effective ways a person can reduce

GUIDELINES FOR ALCOHOL CONSUMPTION

The U.S. Department of Agriculture (USDA) and U.S. Department of Health and Human Services, *Dietary Guidelines for Americans*, 2020-2025, recommends (253):

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.

U.S. Preventive Services Task Force (USPSTF) recommends that clinicians screen adults age 18 and older for alcohol misuse and provide individuals engaged in excessive drinking with brief behavioral counseling interventions. However, according to a recent survey, while many of the survey respondents report being asked by their health care provider about alcohol consumption and binge drinking, during checkups, 80 percent of these individuals received no advice to reduce their drinking (288).

Adapted from (184).

his or her 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. 48).

In the United States, melanoma incidence has been rising for decades—incidence in 2018 was six times higher than it was in 1975 (4,184,296). While ongoing research will determine the relative contribution of UV exposure versus increased screening through skin examinations to this rapid rise in melanoma cases (296), it is vital that all sectors including health care, the federal government, business, advocacy, and communities coordinate efforts to reduce risk exposure for all skin cancers through public health campaigns such as those encouraging sun-protective behaviors as well as evidence-based public policies. Public education regarding skin cancer risk reduction is extremely important considering findings from a recent survey which found that one third of its participants lacked a basic understanding of skin cancer and sun protection practices that can help reduce their risk of skin cancer (297).

As of January 1, 2021, in the U.S., 20 states and the District of Columbia have laws prohibiting tanning for minors (under the age of 18) without exemptions (273). There is evidence that these policies are in fact effective in reducing tanning practice.

WAYS TO PROTECT YOUR SKIN

To reduce your risk of the three main types of skin cancer—basal cell carcinoma, squamous cell carcinoma, and melanoma—the 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 your arms and legs; some clothing is designed to provide protection from the sun

Wear a wide-brimmed hat

Wear wrap-around sunglasses

Avoid indoor tanning with ultraviolet (UV) devices such as sunlamps, sunbeds, and tanning booths

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

American Academy of Dermatology recommends using a sunscreen rated SPF 30 or higher.

U.S. Preventive Services Task Force (USPSTF) recommends that clinicians counsel their lighter-skinned patients ages 6 months to 24 years—or their parents—on limiting exposure to UV radiation to lower skin cancer risk.

Adapted from (172).

A new survey from American Academy of Dermatology found that overall 31 percent of participants, with a higher proportion of younger participants (42 percent of Generation Z and 37 percent of millennials), are unaware that **tanning causes skin cancer** (297).

THE HONORABLE

Michael Burgess, MD

U.S. Representative for Texas' 26th District

"In the 50 years since the enactment of the National Cancer Act we have seen numerous advancements to stop cancer. One of the greatest advancements is the HPV vaccine, a vaccine that prevents the development of certain cervical cancers. My hope is that soon there will be not just a vaccine but a cure for all cancers. Congress must continue to put forward legislation, similar to the work we did on the 21st Century Cures Act, to pave the way for new and innovative cures."

As one example, a 2013 New Jersey legislation banning indoor tanning for those 17 and under led to a 50 percent reduction in the prevalence of indoor tanning among high school students in 2018 compared to 2012 (298). The health and economic benefits of banning indoor tanning are also highlighted in recent studies that estimate the cost benefits of such policies. For instance, in a new analysis, researchers project that a national policy banning tanning beds among the 17.1 million minors ages 14 to 17 years residing in the United States would prevent more than 15,000 melanoma cases and save $205 million in health care costs over their lifetimes (299).

Prevent and Eliminate Infection with Cancer-causing Pathogens

Persistent infection with several pathogens—bacteria, viruses, and parasites that cause disease—increases a person's risk for several types of cancer (see **Table 3**, p. 49). Globally, an estimated 13 percent of all cancer cases in 2018 were attributable to infection, with more than 90 percent of these cases attributable to just four pathogens: human papillomavirus (HPV), hepatitis B virus (HBV), hepatitis C virus (HCV), and *Helicobacter pylori* (300,301). In the United States, about 3 percent of all cancer cases

TABLE 3

CANCER-CAUSING PATHOGENS

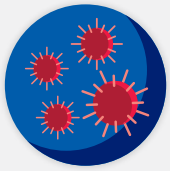
Bacteria		
Pathogen	**Cancer types caused by the pathogen**	**Number of global cancer cases**
Helicobacter pylori	Stomach cancer and non-Hodgkin lymphoma	810,000
Parasites		
Pathogen	**Cancer types caused by the pathogen**	**Number of global cancer cases**
Clonorchis sinensis and Opisthorchis viverrini	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

are attributable to infection with pathogens (181). Individuals can significantly lower their risks by protecting themselves from infection or by obtaining treatment, if available, to eliminate an infection (see sidebar on **Preventing or Eliminating Infection with the Four Main Cancer-causing Pathogens**, p. 50). 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. Despite the availability of a safe and effective vaccine, in the United States, the rate of acute HBV cases as well as the age-adjusted HBV-associated deaths has not changed between 2012 and 2019 (194). Acute infection with HCV is often asymptomatic but more than half of these cases progress to chronic infection. Therefore, it is extremely concerning that the rate of reported acute HCV cases in the United States increased by 89 percent between 2014 and 2019 with most cases occurring among individuals ages 20–39 years (194). Unfortunately, many HCV-positive individuals are unaware of their status (302). Collectively, these data prompted CDC and USPSTF to update their screening recommendation to suggest universal HCV screening at least once in their lifetime for all average-risk individuals ages 18 to 79 years (303,304). Notably, testing for HCV declined by 59 percent in 2020 due to the COVID-19 pandemic compared to prior years (305). While it is reassuring that HCV testing started to rebound later during the year after the first peak of the pandemic, continued public education and policy implementation would be required to prevent any long-term adverse consequences on public health. To eliminate viral hepatitis as a public health threat, 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)* (306). 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

PREVENTING OR ELIMINATING INFECTION WITH THE FOUR MAIN CANCER-CAUSING 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 part of childhood immunization schedule since 1991 • 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. 51)

CDC, Centers for Disease Control and Prevention; MALT, mucosa-associated lymphoid tissue; USPSTF, U.S. Preventive Services Task Force. Adapted from (172).

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 (307). 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 (see **Figure 11**, p. 52). 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 (307). There is emerging evidence confirming that the receipt of guideline-concordant HPV vaccination significantly lowers the risk of infection with HPV types that are covered by the vaccines and dramatically reduces the incidence of cervical cancers among the vaccinated (308–310). According to a recent analysis of data from nearly 1.7 million women from Sweden,

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

HPV vaccination before the age of 17 years was shown to lower the risk of cervical cancer incidence by nearly 90 percent (309). Unfortunately, the uptake of HPV vaccines has been suboptimal in the United States. Even though there has been some progress in the uptake of vaccines 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 (311).

All stakeholders must work together and develop better strategies to increase the uptake of HPV vaccination in the United States. These include increasing health care provider recommendations to 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, a recent clinical trial conducted at 48 pediatric practices across 19 states showed that training pediatric clinicians on strategies on how to communicate with parents led to a reduction in missed opportunities for HPV vaccination and an increase in rates of HPV vaccination initiation (313). However, recent data also show that while more physicians recommended the HPV vaccine to unvaccinated youth in 2018 compared to 2012, even in 2018, half of the more than seven million youth who were eligible for vaccination did not receive a recommendation from their providers (314). Additionally, it is concerning that hesitancy around the HPV vaccine has increased among parents and that misinformation about vaccination is playing a role in the increased hesitancy (314).

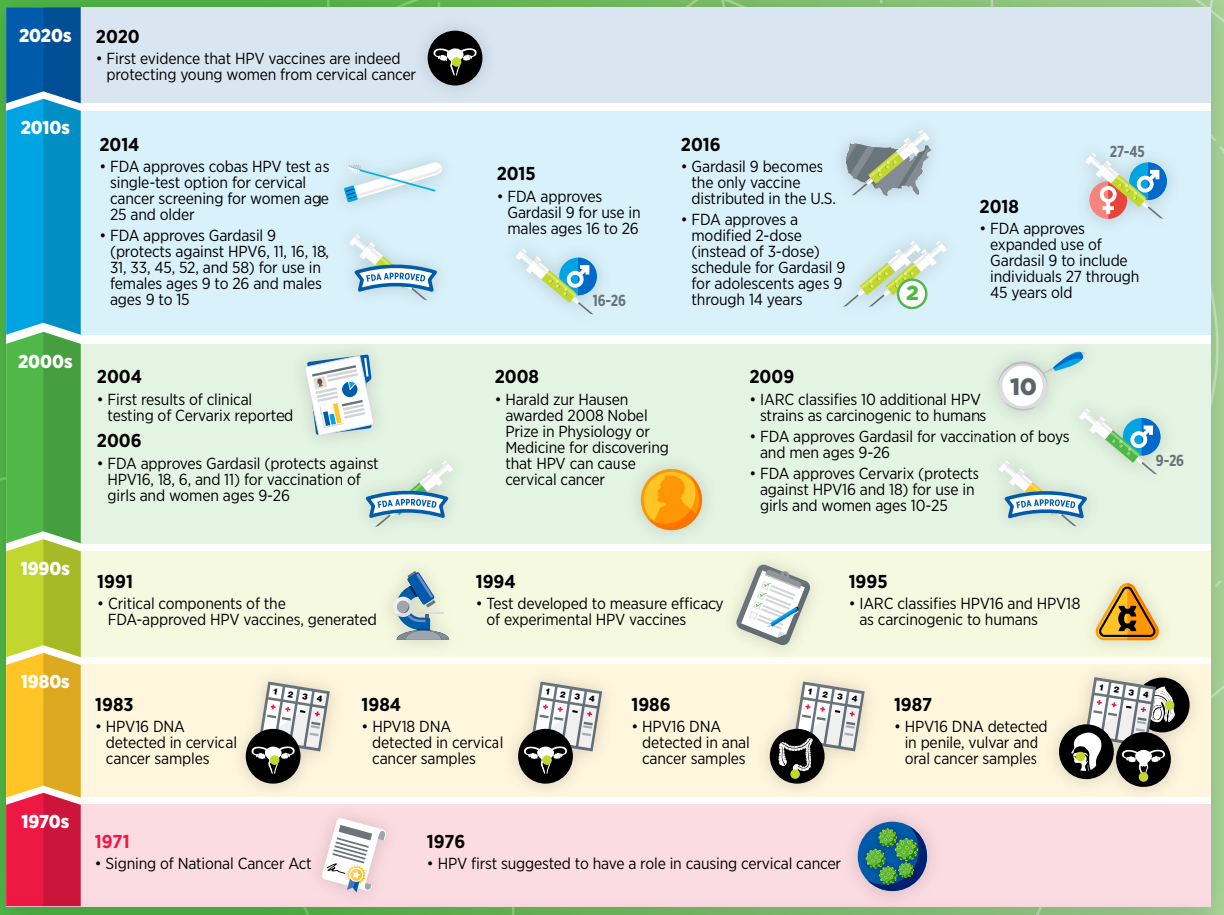
Currently, health care providers across the United States are facing similar challenges with hesitancy and misinformation with regard to the SARS-CoV2 vaccines. To confront the adverse impacts of misinformation, the U.S. Surgeon General has released a public statement to draw attention to this serious public health issue and provide recommendations on how it could be addressed (315). To accelerate our progress against HPV-related cancers and other infectious diseases such as

Cervical cancers in patients of African ancestry have several fold higher prevalence of HPV types which are not covered by Gardasil 9 (such as strains 35 and 59) compared to patients of non-African ancestry (312).

FIGURE 11

NATIONAL CANCER ACT
50 YEARS
1971-2021

50 YEARS OF PROGRESS AGAINST HPV AND RELATED CANCERS



Human papillomavirus (HPV) was first suggested to have an important role in causing cervical cancer in 1976. During the ensuing years, researchers confirmed this hypothesis and identified the cancer-causing strains of HPV. They also found that certain strains of HPV cause many cases of anal, head and neck, penile, vaginal, and vulvar cancers. Thirty years after the first suggestion of a cancer-causing role for HPV, the dedicated efforts of many basic and clinical researchers across the biomedical research enterprise culminated in approval by the U.S. Food and Drug Administration (FDA) of a vaccine that prevents infection with the two most common cervical cancer–causing HPV strains, HPV16 and HPV18, after the vaccine was shown to prevent precancerous cervical abnormalities caused by these strains. Since then, FDA has approved a vaccine, Gardasil 9, which protects against infection with nine different types of HPV and the use of an HPV test called the cobas HPV test as a stand-alone option for cervical cancer screening for women age 25 and older. Research efforts are now focusing on identifying strategies to increase the uptake of HPV vaccination and screening among eligible populations. These efforts include strategies to enhance communication between health care providers and parents to boost vaccination initiation among youth and to simplify the vaccination regimen by determining whether fewer doses of the vaccine can still trigger a sufficient immune response against the virus.

ESTIMATED BY 2030

Annual Cervical Cancer Cases
>700K

Annual Cervical Cancer Deaths
~400K

- In November 2020, WHO launched the Global Strategy to Accelerate the Elimination of Cervical Cancer, outlining three key steps: **vaccination, screening, and treatment.**
- Successful implementation of these strategies **could reduce cervical cancer cases by 40 percent** and **prevent 5 million deaths by 2050**.

COVID-19, it is vital that evidence-based interventions are implemented in both health care and community settings to enhance public trust in vaccination as well as other preventive measures that improve health outcomes.

Be Cognizant of Reproductive and Hormonal Influences

BREASTFEEDING

Studies have shown that having children reduces the risk of a common type of breast cancer, estrogen receptor-positive tumors, in mothers but increases the risk of breast cancers that are estrogen receptor negative (316,317). There is also strong evidence that breastfeeding decreases the risk of breast cancer in mothers (318). Notably, breastfeeding greatly reduces the increased risk of estrogen receptor-negative cancers that are associated with having children. Women who breastfeed also have a lower risk of a particularly aggressive type of breast cancer known as triple-negative breast cancer (319). According to recent data, breastfeeding is associated with a 22 percent reduction in the risk of developing triple-negative breast cancer, whereas weaker or no correlations have been observed with other types of breast cancer (320). Emerging evidence suggests that breastfeeding may also be associated with a lower risk of ovarian cancer, conferring reduction of cancer risk in both white and African American women (321,322). Unfortunately, according to a recent national survey, fewer than 40 percent of U.S. women are aware of the benefits of breastfeeding in reducing cancer risk (323). Increasing public awareness of this information is important if we are to increase breastfeeding initiation among all women. It would also be critical to identify targeted interventions for certain population groups, such as African American women, who have a disproportionately high incidence of triple-negative breast cancer and a lower prevalence of breastfeeding compared to all other U.S. racial and ethnic groups (324,325).

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 occur 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 estrogen plus progestin. 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.

Some of the most 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 estrogen plus progestin have an increased risk of developing breast cancer (326,327). The risk is greater with longer duration of use (328,329). 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 (328). Notably, the increased risks were observed both for white and Black women (330,331). A recent analysis from the United Kingdom corroborated the data from the WHI and showed that treatment with estrogen plus progestin is associated with a 26 percent increase in the risk of breast cancer (332). All 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.

Limit Exposure to Environmental Carcinogens

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 second leading cause of lung cancer death in the United States although levels of naturally occurring radon vary widely based on geographic location within the country (273,333). Other examples of environmental carcinogens include arsenic, asbestos, lead, radiation, and benzene (334). According to the WHO, environmental risk factors account for nearly 20 percent of all cancers globally, most of which occur in low- and middle-income countries.

It can be difficult for people to avoid or reduce their exposure to environmental carcinogens, and 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.

Outdoor air pollution is classified by the International Agency for Research on Cancer (IARC), an affiliate of the WHO, as a potential cause of cancer in humans (336). 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 (195). Therefore, it is concerning that nearly 21 million people in the United States were exposed year-round to unhealthy levels of particle pollution between 2017 and 2019 (195). Communities of color and people living in poverty were at an increased risk of being exposed to polluted air (195). Therefore, new policies to reduce the release of pollutants into the atmosphere are urgently needed to combat the adverse health effects of air pollution.

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 low-income neighborhoods. Similarly, there are disparities in the burden of cancers caused by environmental exposures based on geographic locations and socioeconomic status (337). 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/or more effective policies need to be developed and implemented for the benefit of all populations, especially the most vulnerable and underserved.

A recent analysis using data from **195 countries** around the globe indicated that the **exposure to 12 (out of 13) occupational carcinogens** included in the analysis increased between 1990 and 2017, while exposure to one, asbestos, decreased during the same period (335). Collectively, all thirteen occupational carcinogens **contributed to 319,000 cancer deaths in 2017**, with asbestos, silica, and diesel engine exhaust contributing the highest to the cancer burden.

SCREENING FOR EARLY DETECTION

In this section, you will learn:

- Breakthroughs in understanding how cancer develops and progresses are facilitating the development of cancer screening tests that can detect cancer at its earliest stage before it has spread to other sites.
- Professional organizations and government-affiliated agencies carefully evaluate the benefits and harms of cancer screening to make evidence-based recommendations for its use in the clinic.
- Technological advances, such as state-of-the-art DNA sequencing methods, minimally invasive biopsies, artificial intelligence, and cutting-edge imaging are poised to transform early detection 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 pancreas and liver, for which there are currently no screening tests available for the average risk population.
- The COVID-19 pandemic led to significant declines in cancer screening uptake, and ongoing research will be needed to determine the long-term effects of such decline on future cancer outcomes.

Since the signing of the National Cancer Act in 1971, researchers have made significant strides in decoding the underlying causes of cancer development (see **Understanding How Cancer Develops**, p. 27). In parallel, technological innovations in DNA sequencing and cellular imaging approaches have enabled reliable and reproducible detection of the genetic, molecular, and cellular events that drive cancer initiation and progression. Collectively, these advances have

THE HONORABLE

Donald Payne, Jr.

U.S. Representative for New Jersey's 10th District

"The 50th anniversary of the National Cancer Act of 1971 is a momentous occasion. It created the foundation for cancer research programs that have saved millions of lives through advances in how cancers are diagnosed and treated. I know the dangers of cancer personally. My father, Congressman Donald M. Payne, Sr., died of colorectal cancer. That is one reason I am proud to support cancer research and champion innovative methods for cancer detection, such as blood-based colorectal cancer testing, so we can diagnose cancer more effectively and save more lives."

THE HONORABLE

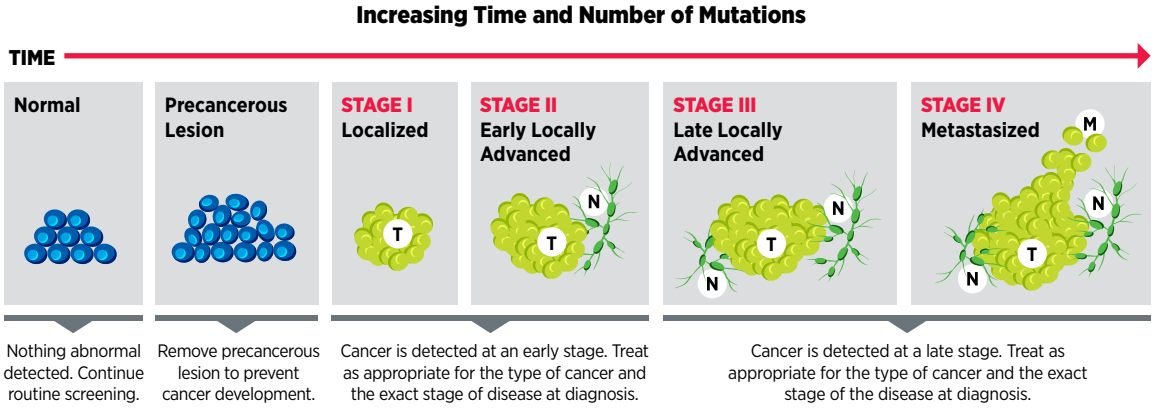
Debbie Wasserman Schultz

U.S. Representative for Florida's 23rd District

"As a cancer survivor, I have come to learn firsthand that early detection saves lives, which is why I continue to champion legislation to guarantee access to breast cancer screenings for women without copay through the PALS Act, and recently introduced new legislation, the Reducing Hereditary Cancer Act, to guarantee access for coverage of genetic testing for inherited cancer mutations. This year is particularly special because as we are celebrating the 50th anniversary of the landmark National Cancer Act (NCA) of 1971, I am finalizing a comprehensive bill aimed at addressing the entire continuum of care for all survivors to ensure that every survivor's needs are addressed. Over the last 50 years we have made great strides in cancer prevention, detection, and treatments, and I will always remain fully engaged in the battle against cancer so that we can one day fully eradicate this dreadful disease."

FIGURE 12

CANCER SCREENING: WHAT CAN BE FOUND? WHAT CAN BE DONE?



Many 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 uncontrollable cell growth), 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 ultimately metastasizes (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, there are several different things that can be found, and different outcomes that 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. If the test detects a precancerous lesion, the lesion can be removed or treated, thus preventing its progression into cancer. If the test finds a cancer at an early stage of development, for example stage I or stage II for a solid tumor, the patient can be treated successfully and has a higher likelihood of 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 and II. Treatment is less likely to be curative if the test detects cancer at a later stage of development, i.e., stage III or stage IV. The approach to actively combating precancer or cancer at the earliest possible stage, also called cancer interception (338), is determined by the type of cancer found by the screening test and the available strategies to intercept that specific cancer.

Adapted from (172,339,340).

accelerated the development of screening tests and examinations that can find aberrations before the cancer arises or can identify cancers at an early stage of development.

What Is Cancer Screening and How Is It Done?

Cancer screening is the evidence-based determination of whether a person has precancerous lesions or cancer before any of its signs or symptoms appear. The key objective is to find an aberration at the earliest possible time during cancer development. Early detection can help health care providers make an informed decision on whether to monitor, treat, or surgically remove precancerous lesions and early-stage cancer before either progresses to a more advanced stage (see **Figure 12**).

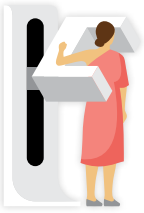
There are different kinds of cancer screening tests and exams that include visual examination to check for unusual features such as

HOW DO WE SCREEN FOR CANCER?

Highlighted below are some cancer screening tests used in the clinic for the five most common cancer types for which there are evidence-based screening guidelines (see sidebar on **Consensus Cancer Screening Recommendations**, p. 63). 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

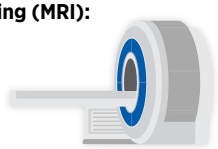
Screening mammogram:



- This test uses X-rays to generate 2-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 3-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.



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).
- Does not directly detect precancerous or cancerous cervical lesions but identifies people for whom further testing is recommended.

Lung Cancer

Low-dose Spiral CT scan:

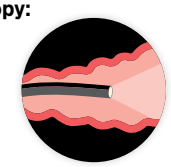
- Uses low doses of X-rays to rapidly image the lungs and detect any structural abnormalities suggestive of lung cancer. Suspicious lesions are then biopsied for diagnosis.

Colorectal Cancer

Stool tests:

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

Flexible sigmoidoscopy and colonoscopy:



- Both use a thin, flexible, lighted tube with a small video camera on the end to allow physicians to look at the lining of certain parts of the colon and rectum.

Computed tomography (CT) colonography (virtual colonoscopy), and double-contrast barium enema:

- Use X-rays to image the colon and rectum.

Blood test:

- Detects epigenetic abnormalities linked to colorectal cancer in blood.
- 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.
- Does not directly detect prostate cancer but identifies men for whom further testing is recommended.

Adapted from (157).

BENEFITS AND POTENTIAL HARMS OF CANCER SCREENING

Benefits of Screening

Reduced cancer incidence

Some screening tests can detect precancerous lesions. Removal of the precancerous lesions can reduce, or even eliminate, an individual's risk of developing the screened cancer at that site (see **Figure 12**, p. 56).

Reduced incidence 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 when the malignancy has spread to other parts of the body and is difficult to treat and/or manage (see **Figure 12**, p. 56).

Reduced cancer mortality

Diagnosis at an early stage of disease can increase the likelihood that a patient can be successfully treated. It can also indicate that making behavioral changes—for example smoking cessation if a screening test finds early signs of lung cancer—will reduce the chances of developing cancer. Both these possibilities increase quality of life and reduce an individual's risk of dying from the screened cancer.

Potential Harms of Screening

Adverse events

Screening tests are medical procedures, and they carry minimal but measurable risks of side effects due to the intervention. It is important to note that U.S. Preventive Services Task Force and other professional societies carefully weigh potential risks of a screening procedure against benefits from cancer screening before recommending a test. Thus, the chance of an adverse event from a recommended screening test is low.

False-positive test results

Researchers are actively identifying new biomarkers that are specific to the cancer an individual is being screened for and are developing innovative approaches to reliably detect these changes in individuals who are at an average risk of developing cancer. It is still possible that some individuals who have a positive screening test result do not have the screened cancer. The rates of false-positive test results vary depending on the test but are generally low. Nonetheless, a false-positive test result can result in additional unnecessary medical procedures, treatments, and anxiety.

False-negative test results

There is also the possibility, albeit low, that some individuals who have a negative screening test result are not free from the screened cancer. A false-negative test result indicating that the individual is free of cancer may lead to missed opportunities for early treatment.

Anxiety

Screening individuals who are not at risk of disease can cause unnecessary anxiety during the waiting period for the test results.

Overdiagnosis and overtreatment

Not all precancerous lesions or cancers detected by screening will go on to cause symptoms and threaten life. Overdiagnosis, as this is called, can lead to overtreatment, which carries its own potential harms and costs. The rates of overdiagnosis and overtreatment vary among cancer types. Additional research is needed to determine which of the early-stage cancers detected through screening are most likely to develop into advanced-stages cancer and threaten life.

lumps or discolored skin; medical and family history analyses to review an individual's genetic, behavioral, and environmental risks; 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 **How Do We Screen for Cancer?**, p. 57).

Recent Advances in Cancer Screening

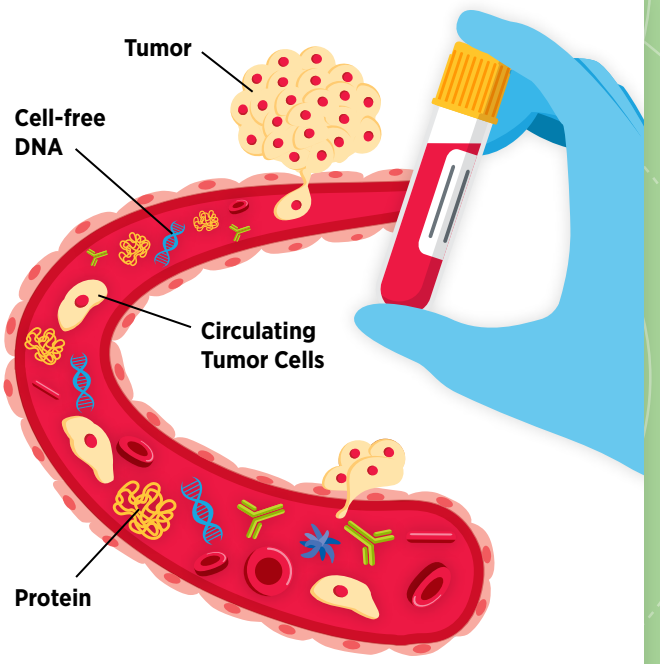
Screening methods are medical procedures that carry the potential of some harm (see sidebar on **Benefits and Potential Harms of Cancer Screening**). Thus, a key area

FIGURE 13

MOVING TOWARD MINIMALLY INVASIVE TESTING

What questions could liquid biopsies answer?

1. Is cancer present? Where is it?
2. Has the cancer spread?
3. What genetic changes does the tumor have?
4. What treatments might work?
5. Are treatments working? Is the cancer becoming resistant to the treatment?
6. Is there any cancer left after treatment?
7. Is there a risk of cancer recurrence?



Research has shown that tumor cells release small amounts of material—cancer cells, cell-free DNA, and lipid-encapsulated sacs called exosomes—into a person's blood or cerebrospinal fluid (341). Furthermore, recent technological innovations in sequencing approaches have enhanced our ability to detect molecular changes reliably and reproducibly using small amounts of DNA or RNA (342). These advances have led to the development of the liquid biopsy, a procedure that is significantly less invasive compared to deriving specimens from the actual tumor tissues. Liquid biopsy involves collection of blood or other biofluids to analyze cells, lipid-encapsulated sacs called exosomes, or cell-free DNA, or potentially other cellular molecules such as RNA or protein, shed by precancerous lesions and tumors. An area of active investigation that is already showing promise is the use of liquid biopsies to screen for early signs of multiple types of cancer at the same time (343). Beyond early detection, liquid biopsies can be used in cancer patients to aid in determining response to treatment and potentially early evidence of relapse when the cancer might be more responsive to other treatments. Extensive research is ongoing to identify biomarkers that can be analyzed using liquid biopsies to detect cancers early, evaluate response to treatment, assess treatment resistance, determine tumor heterogeneity, and monitor minimal residual disease, among other uses (341). The procedure is considered safe and less invasive than tissue biopsy and may be better representative of tumor heterogeneity.

of research focus has been to develop screening methods that are minimally invasive, such as liquid biopsies, thereby further reducing the potential of any harm to the person being screened (see **Figure 13**). Minimally invasive screening tests can potentially increase compliance among individuals who are eligible but forgo recommended cancer screening because of anxiety and/or cultural stigma associated with some screening tests. Additionally, researchers are also investigating whether artificial intelligence (AI) (see **Artificial Intelligence: Shaping the Future of Cancer Science and Medicine**, p. 131), which uses machine learning to analyze vast amounts of data and recognize patterns that are otherwise time-consuming and difficult to find, can be harnessed to increase the speed and accuracy of interpreting results from screening tests.

THE HONORABLE

Tim Scott

U.S. Senator for South Carolina

"On the 50th anniversary of the National Cancer Act, we recognize the incredible progress that has been made in the 'war on cancer.' While there is still more work to be done in combating the disease and reducing health care disparities, the decrease in new cancer cases has made it clear that cancer is on the retreat. I'm honored to stand with you by championing funding and legislation—like the Medicare Multi-Cancer Early Detection Screening Coverage Act—that bring us one step closer to ultimate victory over this disease."

DETECTING EARLY SIGNS OF MULTIPLE TYPES OF CANCER FROM A SINGLE MINIMALLY INVASIVE SCREENING TEST

One area of extensive research in the field of cancer screening is the use of blood-based tests, or liquid biopsy tests, to screen for multiple types of cancer at the same time. There is also emerging data that the multicancer early detection (MCED) approach is feasible and can be used for population-based cancer screening in the clinic (344). MCED tests can detect multiple cancer types by examining specific genetic mutations, epigenetic changes, or other cancer-specific characteristics in the circulating DNA and proteins shed by tumor cells in blood samples. These tests are being investigated for their ability to accurately detect cancers early and to determine whether early detection through these tests can reduce mortality from the cancer for which a person is being screened (345). As one example, a recent study found that an MCED test was able to detect signs of cancer across 50 different cancer types with very high specificity (343). Researchers estimate that actively treating precancerous lesions and/or early-stage cancers detected by this MCED test may help reduce incidence of late-stage cancer development by 78 percent, resulting in a 26 percent decrease in all cancer-related deaths (346).

Researchers involved in the development of a second MCED test performed a retrospective study of women with breast cancer and found that adding the MCED test to the routine breast cancer screening by mammography could have identified 11 percent of women who developed breast cancer that was not captured by routine mammography (347). These studies highlight the enormous promise of liquid biopsies in screening for multiple cancer types in a minimally invasive manner (345).

Additional research is ongoing to ensure that these approaches are safe and effective for routine cancer screening in the clinic, and to evaluate their impact on overall survival following early detection of cancers (348). One area that requires further investigation is the validation of reliable predictive biomarkers and the development of minimally invasive tests to establish evidence-based screening approaches for early detection of cancer types, such as ovarian and pancreatic cancers for which there are currently no available screening tests for average-risk individuals.

ENHANCING THE SPEED AND ACCURACY OF INTERPRETING SCREENING TESTS

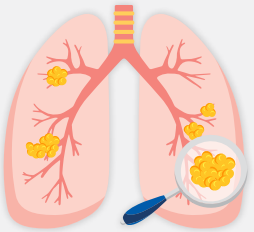
Different cancer screening tests yield different types of results, some in the form of sequencing data and others as pathology or radiology images. Interpretation of cancer screening test results requires a careful analysis by highly trained health care professionals who include primary health care providers, oncologists, pathologists, and radiologists to ensure an accurate determination of next steps. These deliberate safeguards are in place to maximize benefits of cancer screening while minimizing potential harms (see sidebar on **Benefits and Potential Harms of Cancer Screening**, p. 58). However, the process is time-consuming and can sometimes miss signs of cancer.

In recent years, multidisciplinary teams of scientists have been investigating the potential of AI-based approaches in enhancing the accuracy of cancer screening, while simultaneously reducing the time it takes to interpret test results. There are exciting new advances in using AI to improve the accuracy and/or speed of screening for breast, prostate, and lung cancers (349–351). Progress toward routine use of AI in the clinic for cancer screening is underscored by a recent FDA approval of the GI Genius, a medical device that uses AI-based software to assist clinicians in identifying polyps or precancerous lesions during colonoscopy that may not be detectable otherwise (352). Beyond screening for early cancer detection, researchers are exploring the potential of AI in analyzing large genomic and epigenomic datasets to determine whether a specific pattern of genomic and/or epigenomic changes can predict a specific cancer stage, resolving the structure of proteins that are altered in cancer to find regions of the molecule that can be therapeutically targeted, identifying more effective drugs against cancer-specific targets, and improving the accuracy of cancer diagnosis (353–356) (see **Looking to the Future**, p. 130).

Cancer Screening Guidelines

Cancer screening has the potential to save lives by detecting cancer early when it is easier to treat and chances of survival are the highest. As an example, a recent study evaluated the benefit of breast cancer screening over a period of 20 years in more than 150,000 women between the ages of 35 and 64 who had no family or personal history of breast cancer. The results showed a nearly 30 percent relative reduction in breast cancer

2011



Findings from the U.S.-based National Lung Screening Trial (NLST) showed a **20 percent decline in lung cancer mortality** at a 7-year follow-up of more than 50,000 **participants who underwent lung cancer screening** from August 2002 to April 2004 (358).

2020

Findings from the Europe-based Nederlands-Leuvens Longkanker Screenings Onderzoek (NELSON) trial showed a **25 percent decline in lung cancer mortality** at a 10-year follow-up of more than 6,000 **participants who underwent lung cancer screening** from December 2003 to July 2006 (359).

mortality among women age 50 and older who underwent routine mammography, compared to those who did not (357). 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. 58). Because of the potential harms, the risks and benefits of cancer screening are carefully considered for each individual.

Guidelines for cancer screening help individuals decide whether they should be screened for cancer, at what age they should start screening, how frequently they should get screened, and by which method. In the United States, an independent group of experts convened by the Agency for Healthcare Research and Quality of U.S. Department of Health and Human Services 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 the clinic. These volunteer experts form U.S. Preventive Services Task Force (USPSTF). (see **Figure 14**, p. 62)

USPSTF recommendations on cancer screening tests fall into several categories, including recommendations for screening certain individuals at certain intervals, 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 **Figure 14**, p. 62).

As an example, USPSTF reviewed 223 recent studies that analyzed data from more than 86,000 participants before updating its prior guidelines for lung cancer screening in 2021. The new guidelines recommend that former or current smokers start screening annually for lung cancer at an earlier age (50 instead of 55 years) (see sidebar on **Consensus Cancer Screening Recommendations**, p. 63) (360). The new guidelines also reduce the smoking history from 30 pack-years to 20 pack-years; a pack-year equals smoking one pack per day for one year and is a way to measure the amount a person has smoked over a long period of time. The guidelines were revised, in part, because new evidence showed that the previous eligibility criterion for lung cancer screening—adults ages 55 to 80 with a history of 30 pack-years of smoking—was too stringent for African American smokers, who are at a higher risk of developing lung cancer but typically have a smoking history of fewer pack-years, making them ineligible for screening (361).

Several professional societies also convene panels of experts to evaluate data regarding the benefits and potential harms of cancer screening tests, and each society then makes its own evidence-based recommendations about the use of these tests. Not all professional organizations issue screening guidelines for all cancer types. In addition, because the representatives on each panel are often different, and different groups give more weighting to certain benefits and potential harms than other groups do, this can result in differences in recommendations from distinct groups of experts. Despite certain differences in screening recommendations by various subject matter expert panels for the five cancers for which screening is most conducted, there are more commonalities in the guidelines than there are differences (see **Consensus Cancer Screening Recommendations**, p. 63).

Who Should Get Screened and When?

Many factors can contribute to a person's risk of developing cancer, and each person has his or her unique cancer risks. 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. 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.

INDIVIDUALS AT AVERAGE RISK OF DEVELOPING CANCER

Individuals are considered at an average risk of developing cancer if they do not have a family or personal history of cancer and are without any known risk factors that can cause cancer (see **Preventing Cancer: Identifying Risk Factors**, p. 36). Health care providers consider two key characteristics—age and gender—when recommending a cancer screening test to a person who is at an average risk. Because cancer

FIGURE 14

WORKFLOW OF SCREENING GUIDELINES DEVELOPMENT

Review Topic Nominations

Anyone can nominate a new topic for review at any time. U.S. Preventive Services Task Force (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 Evidence-based Practice Center (EPC) develop a research plan and seek expert input on the prioritized topic. USPSTF posts the draft research plan to website for public comments.

Review Public Comments and Finalize Research Plan

USPSTF and EPC carefully review public comments and revise research plan as needed. USPSTF posts the final research plan to 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 to the website, along with EPC evidence review, for public comments.

Review Public Comments & 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.

Panels of subject matter experts, convened by professional organizations and government agencies (such as USPSTF convened by HHS), meticulously review the available evidence, and carefully weigh benefits of cancer screening against any potential harms before recommending at what age a person should be screened, for which cancer type, how frequently, and by which method. Summarized here as an example is the recommendation process followed by the USPSTF.

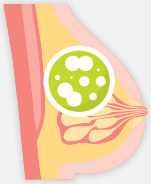
During the development of cancer screening guidelines, the USPSTF is supported by the researchers from the Evidence-based Practice Center (EPC) program, a U.S. Agency for Healthcare Research and Quality initiative under which institutions in the United States and Canada are awarded five-year contracts to serve as EPCs. Once USPSTF decides that a screening guideline merits consideration (cancers for which there are currently no screening guidelines) or revision (for existing guidelines) in light of new scientific evidence, the researchers from the EPC review all relevant scientific literature on potential benefits and harms of screening, which screening method has maximal benefit and minimal harm, age of initiation and frequency of screening, and produce a draft evidence review. The USPSTF uses the draft evidence review to develop a draft recommendation statement. Both documents are made publicly available on the USPSTF website for various stakeholders to provide their feedback. The EPC researchers and the USPSTF review the feedback on the draft evidence review and draft recommendation statement, respectively, and revise the documents if necessary. The final recommendation statement, outlining the new and/or revised guidelines, and the final evidence summary, outlining the reviewed evidence, are posted on the USPSTF website, and published in a peer-reviewed scientific journal.

There are minor differences among different organizations in the process that they use to develop screening guidelines, but the overall rigor that is put in place to ensure maximal benefits and minimal harms for public health and safety is the same.

CONSENSUS CANCER SCREENING RECOMMENDATIONS

The U.S. government-affiliated agencies and many professional societies and organizations have evidence-based recommendations about the use of the screening tests for the five cancers for which screening is most commonly conducted. Here, we highlight consensus, as of July 31, 2021, among these recommendations from U.S. Preventive Services Task Force (USPSTF), American Cancer Society (ACS), National Comprehensive Cancer Network (NCCN), American College of Physicians (ACP), American College of Obstetrics and Gynecology (ACOG), American Urologists Association (AUA), and United States Multi-Society Task Force on Colorectal Cancer (MSTF). Not all professional societies and organizations have recommendations for every cancer screening test.

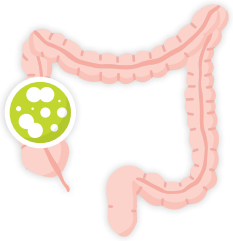
Breast Cancer Screening



There is consensus among the ACOG, ACP, and USPSTF that women ages 50 to 74 who are at **average risk** of developing breast cancer should have regular screening mammograms. However, there is variability about whether this screening should be done every year or every other year.

Some professional societies and organizations, such as ACS, recommend women at **average risk** for developing breast cancer begin regular screening mammograms at age 45; some recommend starting at the even younger age of 40. It is important to note, however, that all the groups support women ages 40 to 49 having the opportunity to have regular screening mammograms if they decide it is right for them.

Colorectal Cancer Screening



There is consensus among ACS, NCCN, and USPSTF that adults ages 45 to 75 who are at **average risk** of developing colorectal cancer should be screened. How often a person should be screened depends on the screening test used (see sidebar on **How Can We Screen for Cancer?**, p. 57).

USPSTF recently revised its guidelines for colorectal cancer screening and now recommends all average-risk individuals should begin screening at the age of 45; the previous recommendation was to start screening at the age of 50. The new guidelines are, in part, issued because of the accumulating evidence that the incidence of colorectal cancer is on the rise among younger adults.

Some professional societies and organizations recommend certain screening approaches over others. The overall message, however, is that using any of the approved tests is better than not being screened and that **average-risk** adults should consult with their health care providers to decide when to start screening and to choose the test that is right for them.

Several groups of individuals are at **increased risk** for colorectal cancer. Colorectal cancer screening recommendations vary for these different groups, but all involve earlier and/or more frequent use of available tests (see sidebar on **How Can We Screen for Cancer?**, p. 57).

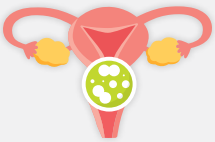
For example:

- NCCN and MSTF on colorectal cancer recommend that individuals at increased risk because they inherited a genetic mutation that causes Lynch syndrome (see **Table 2**, p. 31) should start screening with colonoscopy every 1–2 years at ages 20–25 or 2–5 years prior to the youngest case in the immediate family if it was diagnosed before age 25;
- NCCN and MSTF on colorectal cancer recommend that individuals at increased risk because they have a first-degree relative who has been diagnosed with colorectal cancer should start screening with colonoscopy at age 40 or 10 years before the youngest case was diagnosed, whichever is earlier; and,
- MSTF on colorectal cancer recommends that because African Americans are at increased risk for colorectal cancer, they should begin screening at age 45.

Continued on page 64

CONSENSUS CANCER SCREENING RECOMMENDATIONS *(continued)*

Cervical Cancer Screening

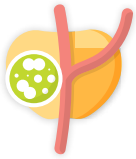


There is consensus among the ACOG, ACP, and USPSTF that:

- **Average-risk** women younger than 21 should not be screened;
- **Average-risk** women ages 21 to 29 should have a Pap test every 3 years;
- **Average-risk** women ages 30 to 65 should have either a Pap test every 3 years, a Pap test and HPV testing every 5 years, or HPV testing alone every 5 years; and
- Women older than 65 should not be screened if they are at **average risk** of the disease because they have previously had regular screenings with normal results and are not otherwise at high risk of developing cervical cancer.

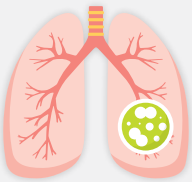
The ACS recommends that women at **average risk** for cervical cancer begin screening at age 25.

Prostate Cancer Screening



There is consensus among ACS, ACP, AUA, and USPSTF that men ages 55 to 69 who are at **average risk** of developing prostate cancer talk to a physician about the benefits and potential harms of PSA testing before deciding if screening is right for them.

Lung Cancer Screening



There is consensus among ACS, NCCN, and USPSTF that annual screening with low-dose spiral computed tomography should be offered to adults ages 55 to 80 who are at **high risk** for lung cancer because of smoking. However, there are differences between USPSTF and the other organizations regarding the age of initiation (50 versus 55) of screening and the criteria for smoking history (at least one pack of cigarettes per day for 20 years or the equivalent vs. at least one pack of cigarettes per day for 30 years, or the equivalent, i.e., two packs per day for 15 years, etc.).

USPSTF has recently revised its lung cancer screening guidelines to lower the age at which individuals at high risk of developing lung cancer should begin screening from 55 to 50 years. The new guidelines also reduce the pack per year history to at least one pack of cigarettes per day for 20 years from at least one pack of cigarettes per day for 30 years. These guidelines expand the population eligible for regular lung cancer screening, including African Americans who are at high risk of developing lung cancer at younger ages even when they have smoked fewer cigarettes for fewer years.

is predominantly a disease of aging, the probability of developing cancer increases with advanced age. In fact, 80 percent of all cancer cases in the United States are diagnosed among those age 55 or older (3). Ongoing research is assessing the optimal age range during which screening individuals who are at an average risk of developing cancer can have maximal benefit. For instance, according to a new report, commencing mammography at age 40 or 41, instead of the currently recommended age of 50, reduced breast cancer mortality by 25 percent in the first 10 years after the start of screening (362). Thus, it is imperative that individuals continually evaluate—and update as needed—their cancer screening plans in routine consultation with their health care providers.

INDIVIDUALS AT HIGH RISK OF DEVELOPING CANCER

Some individuals are at a higher risk for developing certain type(s) of cancer. The reason for an increased risk includes exposure to one or more cancer risk factors (see **Preventing Cancer: Identifying Risk Factors**, p. 36), unique tissue makeup, and/or a family history of cancer. As an example, smoking—an established risk factor for several cancer types—

BREAST DENSITY

What Is Breast Density?

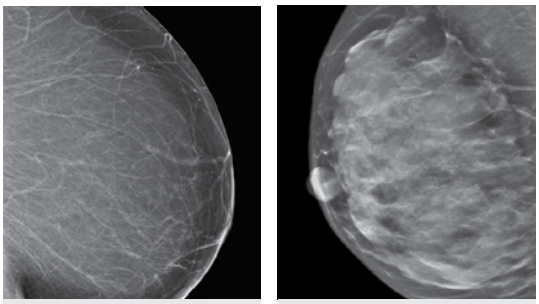
A woman's breast consists of fibrous tissue, which holds the breast in place; glandular tissue, which makes milk; and adipose tissue (fat), which fills the space between fibrous and glandular tissues. Breast density reflects the comparative amounts of fibrous, glandular, and adipose tissues in the breast, as imaged by a mammogram. The higher the amount of fibrous and glandular tissue in the breast and the less fat, the denser the breast tissue appears in the mammogram. Radiologists—the physicians who interpret mammograms—classify breast density using four Breast Imaging Reporting and Data System (BI-RADS) categories:

- The breasts are almost entirely fatty (about 10 percent of women).
- There are few scattered areas of dense fibrous and glandular tissue (about 40 percent of women).
- The breasts are evenly dense throughout (about 40 percent of women).
- The breasts are extremely dense (about 10 percent of women).

The last two categories are considered dense breasts.

Why Is Breast Density Important?

About half of women in their forties have dense breasts. Women with dense breasts are at a higher risk of developing breast cancer compared to women with less dense breast tissue. Furthermore, dense breast tissue, like breast cancer, appears white on mammograms, thus reducing their effectiveness in distinguishing tumor from normal tissue. It is important to note that dense breasts are only one of many risk factors for breast cancer. Ongoing research is focused on understanding why women with dense breasts are at higher risk of developing breast cancer, and whether this knowledge can be used to improve breast cancer risk prediction models. Because of our gaps in knowledge, there is currently no consensus on whether women whose breasts appear dense on mammograms should get additional, if any, breast cancer screening tests.



Nondense breast | **Dense breast**

What Should One Do If One Is Diagnosed with Dense Breasts?

Many U.S. states have enacted legislation requiring health care providers to inform women about breast density in general, or about whether they have dense breasts following a mammogram. Women with dense breasts should talk to their health care providers about whether additional testing with breast tomosynthesis, ultrasound, or magnetic resonance imaging is right for them.

Adapted from (184)

places individuals 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. Another reason why an individual could be at a higher risk is because of the individual's cellular or tissue makeup. For instance, women who have extremely dense breasts have an increased risk of developing breast cancer compared to women with less dense breasts (363) (see sidebar on **Breast Density**).

All individuals at high risk of developing cancer should routinely consult their health care provider team and develop a personalized risk-reducing plan. Some may be able to reduce their risk through behavioral changes, for example, quitting smoking or reducing alcohol consumption. Others may need to increase the frequency of cancer screening or use a test not recommended for average-risk individuals. Some may even consider taking medicine or undergoing surgery to reduce their risk of developing cancer (see **Table 4**, p. 66, and **Supplemental Table 1**, p. 184).

Individuals with Inherited Cancer Susceptibility Syndromes

Some individuals have inherited cancer susceptibility syndromes, a category of disorders in which there is a higher-than-average risk of developing cancer. Also called hereditary cancer syndromes, these disorders are caused by inherited genetic mutations that can predispose an individual to develop certain types of cancer (see **Table 2**, p. 31). If a person thinks that he or she is at a high risk for inheriting a cancer-predisposing genetic mutation, he or she should consult a health care provider and consider genetic

TABLE 4

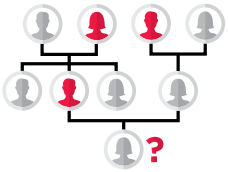
SURGERIES FOR THE PREVENTION OF CANCER

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

HOW DO I KNOW IF I AM AT HIGH RISK FOR DEVELOPING AN INHERITED CANCER?

According to the National Cancer Institute, a person is at an increased risk of developing an inherited cancer if his or her personal/family medical history has one or more of the following features:

- **Cancer diagnosed at a younger age** than usual, such as colon cancer in a 20-year-old.
- **Multiple cancer types diagnosed in the same person**, such as a female with both breast and ovarian cancer.
- **Cancers diagnosed in both of a pair of organs**, such as both kidneys.
- **Several first-degree relatives with the same type of cancer**, such as a mother, daughter, and sisters with breast cancer.
- **Family members with breast** or **ovarian cancer**.
- **Family members with colon cancer** and **endometrial cancer**.
- **Several family members with cancer**.
- **Unusual cases of certain cancer types**, such as breast cancer in men.
- **Presence of birth defects** associated with inherited cancer syndromes (see **Table 2**, p. 31).
- **Race or ethnicity** known to have increased risk of certain inherited cancer syndromes as well as one or more of the above features.

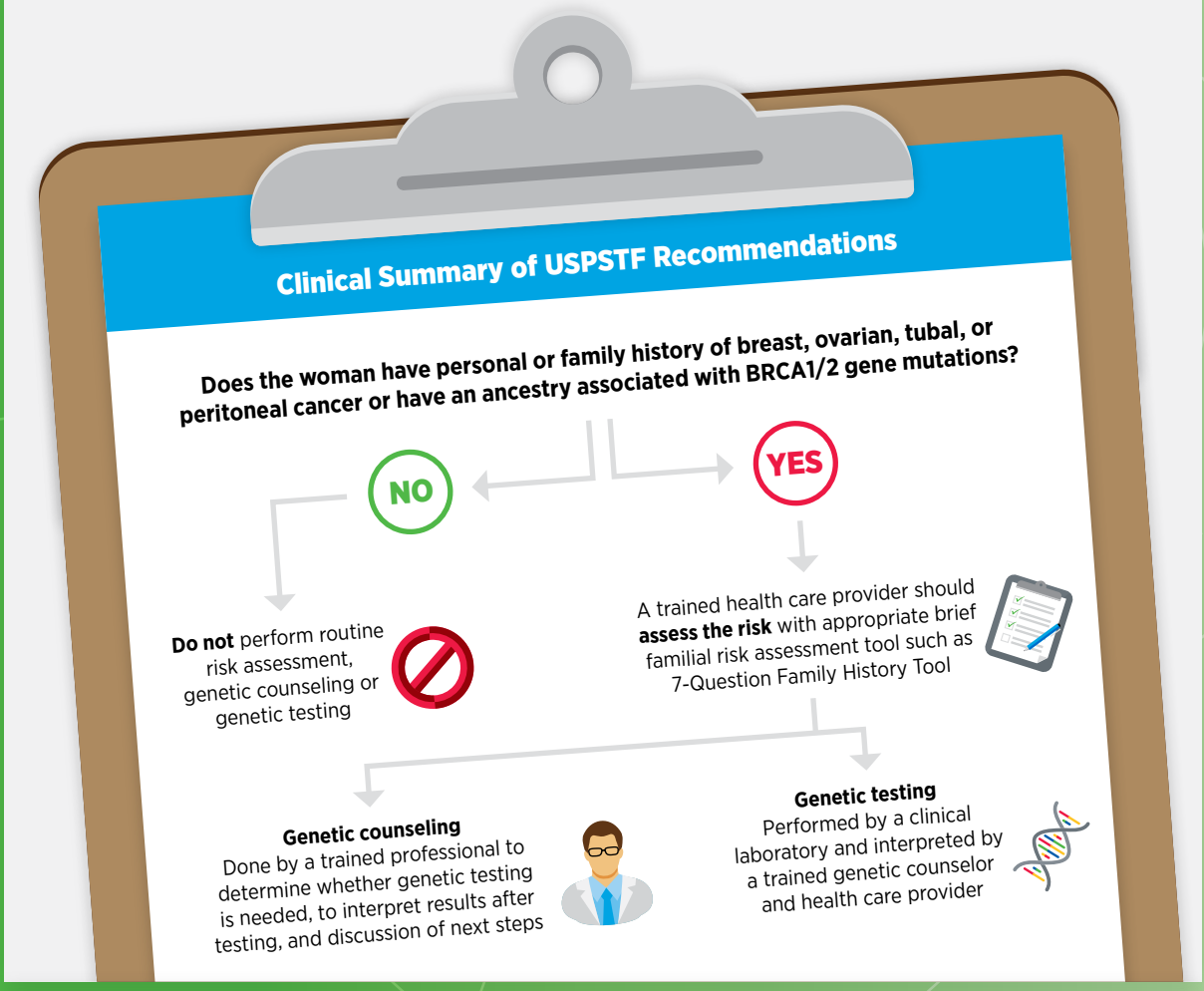


testing (see sidebar on **How Do I Know If I Am at High Risk for Developing an Inherited Cancer?**). As researchers learn more about inherited cancer risk (364), there will be new genetic mutations to test for and changes to the recommendations about who should be offered genetic testing. Therefore, individuals at a high risk of developing inherited cancers should keep an ongoing and informed dialogue with health care providers to make shared decisions about suitability of genetic counseling and genetic testing.

As with other cancer screening tests, the decision of whether to undergo genetic testing, which test to perform, and what follow-up steps should be taken is a complex one. Subject matter expert panels (for instance, USPSTF) and professional organizations (for example, American College of Obstetricians and Gynecologists) issue evidence-based recommendations for individuals with certain cancer susceptibility syndromes to provide guidance for an informed and shared decision-making process (see **Figure 15**, p. 67). Furthermore, several government agencies, including FDA, Centers for Medicare and Medicaid Services, and Federal Trade Commission (FTC), provide regulatory oversight to ensure safety of a genetic test for the individual. It is important to note that there are direct-to-consumer genetic tests that individuals can use without a prescription from a physician, but there are many factors to weigh when considering whether to use one of these

FIGURE 15

THE U.S. PREVENTIVE SERVICES TASK FORCE (USPSTF) RECOMMENDATIONS FOR GENETIC TESTING FOR BREAST CANCER



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

tests. Because of the complexities of these tests, FDA and FTC recommend involving a health care professional in any decision to use such testing, as well as to interpret the results.

Individuals from Certain Racial and Ethnic Minorities

The rapid pace of progress in understanding the genetic and epigenetic basis of precancerous and cancerous aberrations is laying the groundwork for precision cancer prevention (365). At the same time, advances in cancer genetics and epigenetics are also identifying gaps in our knowledge that require additional research to achieve evidence-based health equity for all. One such gap is in our understanding of how mechanisms of cancer onset and progression may differ for individuals from different racial and ethnic population groups.

DISPARITIES IN CANCER SCREENING

There are disparities in the adherence to U.S. Preventive Services Task Force cancer screening recommendations among certain segments of the U.S. population. Complex and interrelated factors contribute to these differences (see sidebar **Why Do U.S. Cancer Health Disparities Exist?**, p. 23). Here, we present some examples of disparities in cancer screening in 2018, the most recent year for which such data are available:

73% vs 61%[1]	Non-Hispanic white women were **significantly more likely to be up to date with colorectal cancer screening**, compared to Hispanic women (368).
80% vs 54%	Women with some form of health insurance were **more likely to be up to date with breast cancer screening**, compared to those without any health insurance (368).
43% vs 28%	Men ages 55 to 69 years with greater than a high school level of education were **more likely to be up to date with prostate cancer screening**, compared to those with less than a high school level of education (369).
24% vs 9%	Vermont residents eligible for lung cancer screening were **more compliant with USPSTF screening recommendations**, compared to those living in Utah (370).
57% vs 70%	According to most recent estimates, adults who met the U.S. Census Bureau's poverty threshold were **less likely to be up to date with their colorectal cancer screening**, compared to those who are above the poverty threshold (332,371).

[1]All percentages in this sidebar are rounded to the nearest integer.

Accruing evidence shows that a breast cancer diagnosis at a younger age is more common in African American women compared to white women. Furthermore, African American women are more likely to be diagnosed with biologically aggressive forms of the disease at all ages (366). This knowledge has raised the possibility that disparities in breast cancer outcomes for African American women can be eliminated by changing the recommendations for mammography and genetic testing based on race and/or ethnicity (367). Another example of cancer health disparity is that African American men tend to develop lung cancer at earlier ages and after fewer pack-years of smoking compared to white men (361). Studies investigating cancer health disparities—such as the examples above—are providing much needed information to develop cancer screening guidelines that are tailored for specific racial and ethnic population groups and are thus more effective in improving outcomes through early detection. However, disparities in the uptake of cancer screening among the underserved segments of the U.S. population remain (see sidebar on **Disparities in Cancer Screening**). These disparities underscore the urgent need for action that includes targeted efforts such as culturally sensitive interventions to raise awareness of the benefits of cancer screening among underserved population groups. In addition, it is important to educate and train clinical researchers and coordinators involved in designing and conducting clinical trials about best practices on how to recruit individuals from diverse and underrepresented population groups, as well as to encourage racial and ethnic minorities to participate in clinical studies on cancer etiology, prevention, and early detection.

Suboptimal Use of Cancer Screening Tests

Even though the benefits of screening for breast, cervical, colorectal, and lung cancer outweigh the potential risks for

SUBOPTIMAL USE OF CANCER SCREENING TESTS

Not all people for whom cancer screening is recommended are up to date with U.S. Preventive Services Task Force recommended screening guidelines. In addition, some people for whom screening is not recommended, such as individuals above the recommended age range for a given cancer screening test, often get screened. The following are selected examples of suboptimal uses of cancer screening tests based on recent data:

33%	**33 percent[1] of adults ages 50–75** were not up to date with colorectal cancer screening in 2018 (374).
28%	**28 percent of women ages 50–74** were not up to date with breast cancer screening in 2018 (374).
82%	**82 percent of adults ages 55–80**, with a 30+ pack-year smoking history who currently smoke or have quit within the past 15 years, were not up to date with lung cancer screening in 2018-2019 (370).
20%	**20 percent of women ages 21–65** were not up to date with cervical cancer screening in 2018 (368).
74%	**74 percent of women ages 75 and older** (above recommended age) received screening for breast cancer in 2018 (375).
59%	**59 percent of men ages 76 and older** (above recommended age) received screening for colorectal cancer in 2018 (375).
65%	**65 percent of women ages 30-65** were overscreened (more frequently than recommended for this age group) for cervical cancer in 2013-2014 (376).

[1]All percentages in this sidebar are rounded to the nearest integer.

defined groups of individuals (see sidebar on **Consensus Cancer Screening Recommendations**, p. 63), many of those for whom screening is recommended do not get screened (see sidebar on **Suboptimal Use of Cancer Screening Tests**). Individuals who are not up to date with cancer screening recommendations are disproportionately found in medically underserved segments of the U.S. population (see sidebar on **Disparities in Cancer Screening**, p. 68).

In addition to the suboptimal uptake among those individuals who should get screened, some people for whom screening is not recommended, such as individuals below or above the recommended age range for a given cancer screening test or those with limited life expectancy, are screened even though the evidence indicates that the benefits of screening are unlikely to outweigh the potential harms for them (see sidebar on **Suboptimal Use of Cancer Screening Tests**).

These challenges have been exacerbated in the past two years due to the ongoing COVID-19 pandemic, which led to a sharp decline in cancer screening during its initial peak. It will be important to continue monitoring whether the substantial decrease in cancer screening leads to any long-term changes in U.S. cancer mortality (372,373) (see sidebar on **Cancer Screening During the COVID-19 Pandemic**, p. 70).

The suboptimal use of cancer screening tests, especially among racial and ethnic minorities, underscores the requirement for new approaches and public policies to increase cancer screening awareness, accessibility, and affordability. As an example, findings from a new study show that individuals

CANCER SCREENING DURING THE COVID-19 PANDEMIC

The COVID-19 pandemic has affected all aspects of cancer research and care. At the onset of the pandemic, elective medical procedures, including cancer screening, were largely postponed to prioritize urgent needs and to reduce the risk of the spread of COVID-19. As a result, there was a large decline in cancer screening in the early months of the pandemic. Below are a few examples of how COVID-19 impacted cancer screening and diagnosis:

99% decline	A 99 percent decline was **observed in mammography rates** in April 2020 when compared to the same time frame in 2019 (379).
82% decline	An 82 percent decline was observed in **HPV test rates for cervical cancer screening** among women ages 30-65 years in March-June, 2020, when compared to the same time frame in 2019 (380).
20%-30% fewer	20 to 30 percent fewer **men were diagnosed with cancerous or precancerous lesions of the prostate** in March-June, 2020, when compared to the same time frame in 2019 (372).
90% decline	A 90 percent decline was observed in **colonoscopy rates** between March 13, 2020, when the national emergency was declared, and early May 2020 (381).
80% decline	An 80 percent decline was observed in **low-dose computed tomography scans for lung cancer screening** in March-June, 2020, when compared to the same period in 2019 (372).

Although most of the above studies indicate that rates of cancer screening may be returning to their prepandemic levels (372,381), the long-term adverse impacts of missed screening and late diagnosis on cancer outcomes need to be monitored.

who received a series of text messages about the importance of colorectal screening, along with free at-home kits for a fecal immunochemical test, had a nearly 10-fold increase in screening completion, compared to those individuals who only received one text reminding them of an overdue screening test (377). Another recent study evaluated the preference of average-risk individuals for different colorectal cancer screening tests (see sidebar on **How Can We Screen for Cancer?**, p. 57). Nearly two thirds of all participants, and half of Hispanic and non-Hispanic African American participants, preferred stool-based tests over colonoscopy. Preference for stool-based tests was also higher among younger individuals (ages 45 to 54 years) and among those without insurance because the test is less expensive than colonoscopy (378). It is important to note that any abnormality identified by a stool-based test still requires follow-up confirmatory tests, such as through colonoscopy, as well as the removal of any precancerous lesions. Nonetheless, these findings underscore the need to develop cancer screening outreach strategies that are based on sociodemographic characteristics, awareness and use of minimally invasive screening methods, and access to preventive health care services.

At the federal level, NCI and CDC play important roles in raising awareness for cancer screening. The NCI's colorectal cancer outreach and screening initiative—Screen to Save—is one example of how government agencies can help increase overall cancer screening rates and reduce cancer health disparities. The Screen to Save initiative aims to provide culturally tailored, evidence-based colorectal cancer information, education, and screening resources within racially and ethnically diverse and rural communities through recruitment of community health educators. Government-mandated health insurance is another effective mechanism to increase the utilization of preventive health services. For example, a recent study found that health insurance coverage mandated by the 2010 Affordable Care Act increased the probability of being up to date on colorectal cancer screening by three percent (382). Although each of the approaches, programs, and policies discussed here is raising awareness of and accessibility to cancer screening, a concerted and coordinated effort to maximize their impact is needed to achieve the vision of cancer health equity.

DISCOVERY SCIENCE DRIVING CLINICAL BREAKTHROUGHS

In this section, you will learn:

- Genetic and epigenetic characteristics of cancer cells, unveiled by discovery science, are being leveraged to develop novel and innovative treatments for cancer.
- Clinical breakthroughs across all pillars of cancer treatment—surgery, radiotherapy, chemotherapy, molecularly targeted therapy, and immunotherapy—are saving and improving lives.
- There is an urgent need of clinical trials to include patients from diverse ethnic and racial backgrounds to fully realize the potential of precision medicine.
- From August 1, 2020 to July 31, 2021, FDA has approved 16 new anticancer therapeutics that include a revolutionary therapeutic against an altered form of the long intractable protein, KRAS, for certain patients with lung cancer, and the first adoptive cell therapy to treat patients with multiple myeloma.
- During the same period, FDA has expanded the use of 11 previously approved anticancer therapeutics to treat additional cancer types, bringing the promise of research-driven clinical breakthroughs to more patients.

Breakthroughs across the spectrum of cancer science and medicine are improving survival and quality of life for patients around the globe. These advances against cancer are driven by concerted efforts from stakeholders working throughout the medical research cycle (**Figure 16**, p. 73).

Medical Research

Medical research is a hypothesis-driven, years-long process with the goal of refining and improving clinical care for all individuals (see **Figure 16**, p. 73). Researchers use a new discovery or observation at any step of the medical research cycle as a basis to develop a hypothesis. The hypothesis addresses one or more questions, with the potential to improve the practice of medicine or public health, through experiments in a wide range of models that mimic healthy and diseased conditions. Findings from these experiments can lead to new therapeutic targets, inform potential preventive interventions, identify approaches for early diagnosis, or uncover predictive or prognostic biomarkers, each of which has the potential to drive clinical care forward. Once a potential therapeutic target is identified, several candidate therapeutics against the target are rigorously tested to determine the appropriate dosage, dosing schedules, and potential toxicities (see sidebar on **Therapeutic Development**, p. 74). These preclinical studies help determine the most promising candidates, which are then tested in a clinical trial.

CLINICAL STUDIES

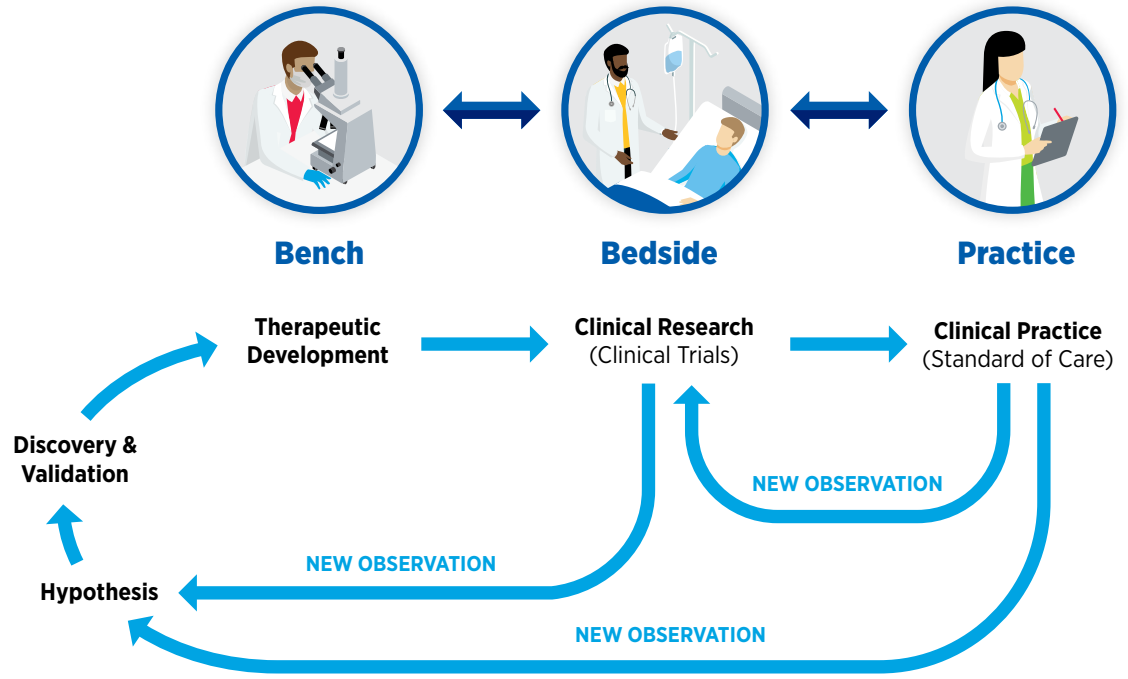
Clinical studies are the backbone of medical research and, together with basic research, provide the foundational knowledge to bring safe and effective medicines to patients in a timely manner. Evidence gathered from clinical studies, also called clinical trials, is reviewed by FDA to determine whether a therapeutic should be approved for use in the clinic. There are many types of clinical trials and each is designed to address different research questions (384) (see sidebar on **Types of Clinical Trials**, p. 75). Because clinical trials involve the use of experimental therapeutics and aim to derive conclusions for the entire population based on data from a cohort of participants, their design and conduct are reviewed and approved by institutional review boards. Clinical trials are closely monitored throughout the duration of the study to ensure safety of the participants.

Clinical trials testing the efficacy and safety of candidate anticancer therapeutics are traditionally conducted in three consecutive phases (see **Figure 17**, p. 76). This approach requires substantial investment, thousands of participants, and many years to complete clinical trials. The result is a lengthy and costly undertaking that poses major barriers to rapidly translating discoveries into clinical advances.

To reduce the length of time it takes for patients to access new treatments for life-threatening diseases such as cancer, 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. In the past three decades, FDA has introduced expedited review processes to minimize approval times for promising new therapeutics. According to a recent study examining FDA approvals of anticancer drugs from 2012 to 2017, the approval time through accelerated review process took an average of six years compared to more than eight years for regular approvals

FIGURE 16

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 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 (see sidebar on **Therapeutic Development**, p. 74). 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 for the patient and effective against the type of cancer for which it is designed, 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, the observations from the preclinical and/or clinical testing can spur future research efforts.

Adapted from (383).

during the same period (385). While the expedited review processes have substantially shortened the time that it takes for novel anticancer therapeutics to reach patients, long-term studies are needed to confirm whether therapeutics approved through these pathways result in increased overall survival and/or improved quality of life for cancer patients.

Progress across the continuum of cancer research and care is also improving the design and execution of clinical trials. In 2018, FDA issued guidance for researchers and the pharmaceutical industry to adopt an improved design for clinical trials. The new strategy—also called the master protocol design—proposes an adaptive and seamless approach to conducting clinical trials for testing the efficacy and safety of new anticancer therapeutics (388).

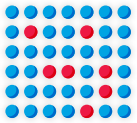
Master protocol design aims to streamline clinical trials by:

1. Matching the right therapeutics with the right patient more quickly;
2. Reducing the number of patients needed to test the efficacy and safety of the drug; and

THERAPEUTIC DEVELOPMENT

Target discovery and validation

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

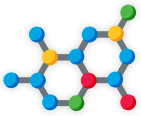


Target to hit

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

Hit to lead

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



Lead optimization

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

Preclinical testing

Cell-based and animal models are used to test for effectiveness of the optimized lead, identify potential toxicity issues, and determine an optimal starting dose and dosing schedule for clinical or "first-in-human" testing. The final compound is called the clinical candidate.

Investigational new drug (IND)

Prior to clinical testing, one or more clinical candidates are assessed in rigorous good laboratory practice (GLP) studies with the drug product generated through good manufacturing practices (GMP) and then submitted to the U.S. Food and Drug Administration (FDA) for approval for use in clinical trials.

Adapted from (129).

3. Decreasing the length of time it takes for a new anticancer therapeutic to be tested and made available to patients if the trial shows it is safe and effective (389).

Furthermore, the master protocol design addresses multiple questions within a single overall clinical trial. Advances in our understanding of the genetic mutations that drive cancer development are further helping to shape clinical trial design. As an example, "basket" trials allow researchers to test one anticancer drug in a group of patients with a common genetic mutation against which the drug is targeted, regardless of the tissue of origin of the cancer (386) (see **Figure 18**, p. 77).

Despite improvements in both the clinical trial design and drug approval 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, has also offered a blueprint of success to further revise and reform the clinical trial enterprise and the drug approval process for the benefit of cancer patients (see the sidebar on **Lessons from COVID-19 to Streamline Oncology Clinical Trials**, p. 78).

The urgency with which all stakeholders have come together and shared data and resources like never before, led to the unprecedented speed of vaccine development against SARS-CoV-2 (391), the virus that causes COVID-19. However, there are still many challenges that need to be addressed. One of the most pressing challenges is that racial and ethnic minorities continue to be significantly underrepresented in many clinical trials, including those

TYPES OF CLINICAL STUDIES

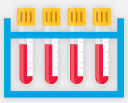
There are multiple types of clinical studies (also called clinical trials). Although each clinical trial is designed to address specific research questions, many clinical studies can also provide answers to additional questions. For example, treatment trials, which primarily determine clinical outcome such as efficacy of a drug for treating the cancer type for which the drug has been developed, can also evaluate measures to assess the impact of the treatment being tested on quality of life. In oncology, the types of clinical trials include:

Prevention trials

Designed to find out whether healthy people can reduce their risk of cancer by preemptively taking certain actions, such as quitting smoking; by taking certain therapeutics, vitamins, minerals, or dietary supplements; or by having certain risk-reducing surgeries.

Screening trials

Designed to evaluate new tests to detect cancer in individuals before symptoms arise, with the goal of determining whether the screening test can reduce deaths from the cancer being screened for.



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 are safe and efficacious for people who have cancer. These trials can test any type of treatment, including surgery, radiotherapy, cytotoxic chemotherapy, molecularly targeted therapy, and immunotherapy, alone or in combination with another treatment(s).

Quality of life trials (also known as supportive care or palliative care trials)

Designed to examine whether people who have cancer can improve their quality of life by taking certain actions, such as attending support groups or exercising more; or by taking certain therapeutics, such as those to treat depression or nausea.

Natural history or observational studies

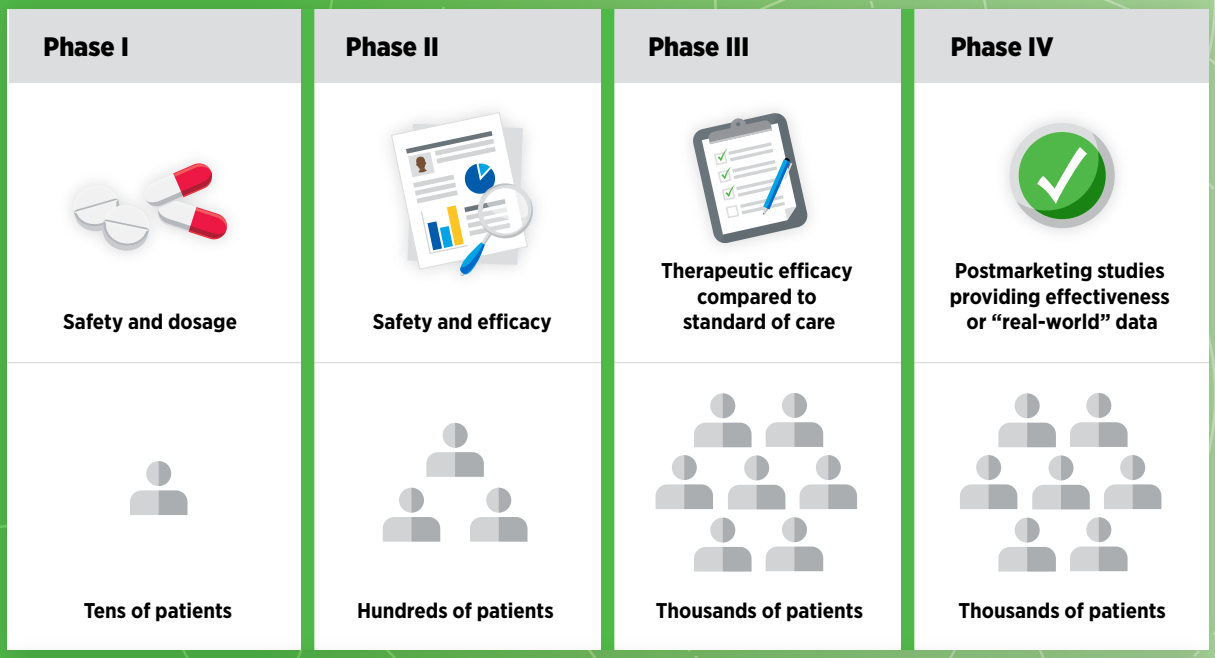
Designed to learn more about how cancer develops and progresses by following people who have cancer or people who are at high risk for developing cancer over a long period of time.

Correlative studies

Designed to examine the relationship between potential efficacy of candidate anticancer therapeutics and positive clinical activity as determined by biomarkers. Correlative studies are an integral part of early-stage clinical trials when the effects of a candidate anticancer therapeutic on key clinical outcomes, such as reduction in tumor size, may not be apparent. Data obtained from correlative studies can provide important guidance on the design and ultimately successful evaluation of anticancer therapeutics in later stage trials.

FIGURE 17

PHASES OF CLINICAL TRIALS



Oncology clinical trials—the types of clinical studies that evaluate the efficacy and safety of potential new therapeutics for treating cancer patients—have traditionally been conducted in three successive phases, each with an increasing number of patients. Phase I studies determine the optimal dose of an investigational anticancer therapeutic, how humans metabolize it, and any potentially harmful side effects. Phase II studies determine the initial efficacy of an investigational therapy in humans while continually monitoring for potential toxicities. Phase III studies are large trials designed to determine therapeutic efficacy of the new drug in comparison to standard of care. When successful, the results of these trials can be used by the U.S. Food and Drug Administration (FDA) to approve new therapeutics or new indications for existing therapeutics. Phase IV studies are conducted after a therapy is provisionally approved by FDA and provide additional effectiveness or "real-world" data on the therapy.

testing new anticancer therapeutics and the COVID-19 vaccines (see sidebar on **Disparities in Clinical Trial Participation**, p. 79). This lack of diversity, perpetuated in part by systemic and structural racism, poses a threat to the promise of equitable personalized medicine for all. It is imperative that stakeholders across the continuum of cancer science and medicine come together to increase diversity in clinical trial participation. This vision can be achieved by developing multipronged strategies that include, among others, educating clinical researchers about approaching and encouraging patients from diverse backgrounds to participate in clinical trials; simplifying eligibility criteria and logistics for patients to participate in clinical studies; and implementing effective education and policy initiatives aimed at reducing hesitancy among racial and ethnic minorities to participate in clinical research.

Progress Across the Spectrum of Cancer Treatment

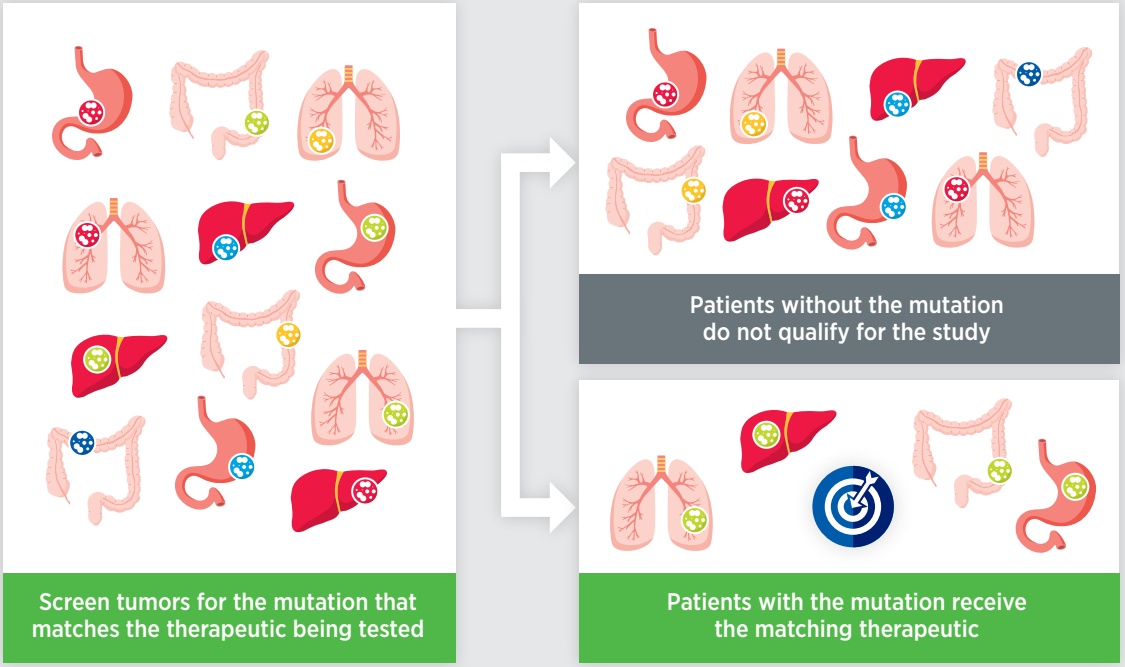
Discovery science continuously drives breakthroughs in cancer etiology, prevention, detection, diagnosis, treatment, and survivorship. Clinical breakthroughs that lead to the FDA approval of anticancer therapeutics and medical devices, in turn, accelerate the pace of the medical research cycle through new real-world observations (see **Figure 16**, p. 73) (see **Supplemental Table 2**, p. 185, and **Supplemental Table 3**, p. 189). The overall goal is to refine and/or expand the five pillars—surgery, chemotherapy, radiotherapy, molecularly targeted therapy, and immunotherapy—that constitute the current paradigm for cancer treatment (396) (see **Figure 19**, p. 80).

This section primarily discusses 16 new anticancer therapeutics, three new diagnostic imaging agents, and two

FIGURE 18

MASTERING CLINICAL TRIAL DESIGN

Basket Trials



Recent advances in our understanding of cancer biology have led to new ways of designing and conducting oncology clinical trials. One of the new approaches is to use a master protocol to answer multiple questions within a single overall clinical trial. Basket trials are one type of master protocol clinical trial. In the basket trial depicted here, one drug is being tested against liver, lung, colon, and stomach cancers characterized by a particular genetic mutation (green dots). This precision approach expedites the clinical testing of new anticancer therapeutics by matching the treatment with the right patients at the start of the trial. The result of this strategy is streamlined clinical studies that reduce the number of patients who need to be enrolled in the trial before safety and efficacy of the tested anticancer therapeutic is determined, and/or decrease the length of time it takes for a safe and efficacious new anticancer therapeutic to be tested and made available to patients (386). The National Cancer Institute–Molecular Analysis for Therapy Choice (NCI-MATCH) trial is one example of a basket clinical trial design. The NCI-MATCH trial is the first national-scale precision medicine trial that incorporates centralized diagnostic testing and dozens of treatment options in parallel. Patients enrolled in the NCI-MATCH trial are assigned to receive treatment based on genetic mutations present in their tumors (387).

new medical devices approved by FDA during the time frame—August 1, 2020 to July 31, 2021—covered by this report. Also highlighted are the 11 previously approved anticancer therapeutics that were approved by FDA for treating additional types of cancer during the same time (see **Table 5**, p. 81, and **Supplemental Table 4**, p. 191). 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 cancer, it is also important to note that not all patients receive and/or benefit from the care recommended for the type and stage of cancer for which they have been diagnosed. Gaps in equitable and affordable access to cancer treatment for patients from

LESSONS FROM COVID-19 TO STREAMLINE ONCOLOGY CLINICAL TRIALS

The guidance issued by FDA and NCI during 2020 to minimize the adverse effects of the pandemic on the conduct of cancer clinical trials offers valuable lessons that can be implemented to streamline future oncology clinical trials, increase participation from diverse groups, and accelerate the pace of progress against cancer. These lessons include:

Consenting remotely using electronic means to participate in a clinical trial.

Currently, in-person consent is required to participate in an oncology clinical trial.

Allowing the use of any laboratory and imaging centers that meet the specifications required for participation in a clinical trial.

Currently, individuals are required to use a clinical trial-specified laboratory or imaging center.

Permitting telehealth approaches for routine clinical assessments, such as safety of the experimental treatment.

Currently, individuals are required to visit clinics in person for these evaluations.

Increasing the engagement of community-based network sites in conducting a clinical trial.

Currently, experimental therapeutics are only available at the institutes where clinical trials are taking place.

Delivering experimental drugs directly to patients.

Currently, an in-person visit is required to receive experimental drugs.

Making clinical trials more accessible to underserved populations and those living in rural areas.

Currently, underserved populations have limited access to clinical trials for a variety of reasons.

Developed from (390).

all walks of life can result in adverse survival rates that disproportionately affect certain population groups (sidebar on **Disparities in Cancer Treatment**, p. 82). It is essential for stakeholders across the cancer research continuum to urgently and collectively address these disparities if the vision of equitable cancer care is to be realized.

In addition to the existing challenges in the delivery of cancer treatment, the COVID-19 pandemic has created some unique barriers for patients during the past two years. The setbacks from the COVID-19 pandemic on screening rates for various cancer types are likely to have long-term effects on late-stage cancer diagnosis and outcomes for patients. In terms of treatment, cancer patients have experienced serious interruptions across all five pillars of the cancer treatment paradigm, for example, cancellations of anticancer therapies that can only be administered in a medical facility (see sidebar on **The Impact of COVID-19 on Cancer Treatment**, p. 83). COVID-19 has also highlighted areas where lessons learned from the pandemic can help revise cancer treatment and care strategies to improve the lives of cancer patients. For example, the pandemic has spurred a shift toward telehealth, which is the distribution of health-related services from health care providers to patients using telecommunication technologies (407). Another effect of the pandemic on cancer care is the rethinking of when and how anticancer therapeutics are administered. Over the past year, FDA has taken several steps that can reduce the number of times a patient must visit a health care facility for cancer treatment. For example, in April 2020, the agency approved an alternative dosing schedule for the immunotherapeutic pembrolizumab (Keytruda), which is approved for treating a wide array of cancer types (see **Releasing the Brakes on the Immune System**, p. 107). Pembrolizumab is administered intravenously, meaning

DISPARITIES IN CLINICAL TRIAL PARTICIPATION

To fully ensure the safety and efficacy of anticancer therapeutics for everyone who will use them once approved, it is vital that the participants in the clinical trials represent the diversity of the patient population. Despite this knowledge, several segments of the population are underrepresented in clinical trials relative to their proportion in the overall population and/or the relevant disease population. Examples of these disparities include the following:

Only **2.47%**	African Americans accounted for **only 2.47%** of participants in clinical trials for oral chemotherapeutic agents between 2009 and 2019, while they make up 13.4% of the total U.S. population (392).
Only **0.5%**	American Indians/Alaska Natives accounted for **only 0.5%** of participants in clinical trials for prostate cancer, while they make up nearly 2% of the total U.S. population (393).
Only **14.7%**	Breast cancer patients age 65 and older accounted for **only 14.7%** of participants in clinical trials between January 1999 and January 2019, while this age group has the highest incidence of breast cancer (394).
50% less likely	Adolescent and young adult cancer patients of Hispanic origin were **50% less likely to participate in clinical trials** compared to non-Hispanic white patients (395).

that patients must travel to a health care facility to receive the treatment. The new dosing regimen of 400 mg of pembrolizumab every six weeks provides an alternative to the standard 200 mg every three weeks (408). In September 2020, FDA approved azacitidine (Onureg) as maintenance therapy for patients with acute myeloid leukemia (AML) in a tablet form, making it easier for adult AML patients to manage their disease effectively without the need to visit a health care facility for the traditional intravenous administration of the drug. As a result, cancer patients have experienced, among other benefits, reduced travel, decreased social anxiety associated with hospital visits, and increased financial savings.

ADVANCES IN CANCER TREATMENT WITH SURGERY

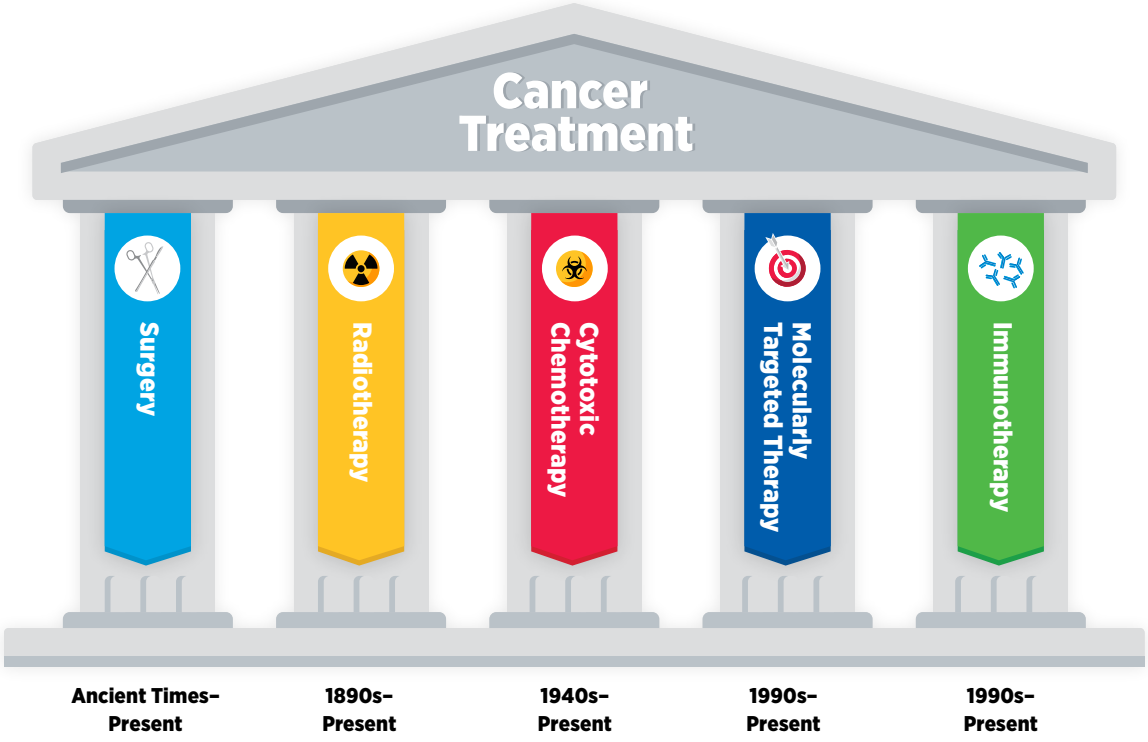
Surgery was the only available treatment for cancer for centuries (see **Figure 19**, p. 80) and remains an important treatment option for many patients (see sidebar on **Using Surgery in Cancer Care**, p. 86). A recent study shows that the global demand for surgery to treat cancer will increase by 52 percent by 2040 (413). Researchers are continuously innovating new and improved

THE HONORABLE
Chris Van Hollen
U.S. Senator for Maryland

"While millions of families across America are battling cancer, millions more have been saved or are leading much longer lives because of past research to treat and defeat this disease. On this 50th anniversary of the National Cancer Act, we should celebrate the progress we have made in the fight against cancer, and re-dedicate ourselves to winning that fight. To that end, we must dramatically boost our investment in research to prevent cancer, detect and diagnose it early, and continue to develop therapies and cures to save lives."

FIGURE 19

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 (397). In 1896, treatment of a breast cancer patient with X-rays added radiotherapy as the second pillar (398). The foundations for the third treatment pillar—cytotoxic chemotherapy—were established in the early 1940s when a derivative of nitrogen mustard was explored as a treatment for lymphoma (399). 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 fourth pillar, molecularly targeted therapy (400). Also, in the late 1990s, decades of discovery science laid the groundwork for the fifth treatment pillar, immunotherapy (401). Continued evolution of new approaches, such as analysis of tumors aided by AI, enhanced molecular imaging, and validation of new biomarkers, plays a critical role in the development of each of these therapeutic areas.

strategies to maximize the benefit and minimize harms from surgery for cancer patients.

As new treatments are added across the pillars of cancer treatment (see **Figure 19**, p. 80), a common approach to treating patients with cancer has been to use surgery alongside one or more classes of therapies available for the diagnosed cancer type. For many cancers, a multidisciplinary team including surgical, medical, and radiation therapy oncologists as well as other individuals as appropriate (e.g., other medical specialists, nurses, social workers) reviews treatment options and makes recommendations for treatment. Sometimes, additional therapy is given prior to surgery (neoadjuvant), both before and after surgery (perioperative), or after surgery (adjuvant) with the decision based on specifics of the situation. (414). The primary goal of these therapies is to eliminate any cancer cells that surgery might not remove. When given in the neoadjuvant or perioperative setting, they may also improve the surgeon's ability to remove the tumor. Researchers have found that neoadjuvant, perioperative, and adjuvant therapies can significantly increase overall survival (see **Table 6**, p. 87) and/or quality of life in the appropriate clinical settings (414).

TABLE 5

NEWLY FDA-APPROVED ANTICANCER THERAPEUTICS: AUGUST 1, 2020-JULY 31, 2021

Approved Indication	Generic Name	Trade name	Formulation
Angiogenesis Inhibitors			
Certain type of kidney cancer	tivozanib	Fotivda	
Cell-signaling Inhibitors			
Certain type of lung cancer	amivantamab-vmjw†	Rybrevant	
Certain type of non-Hodgkin lymphoma*	crizotinib†	Xalkori	
Certain types of lung and thyroid cancers	pralsetinib†	Gavreto	
Certain type of lung cancer	tepotinib	Tepmetko	
Certain types of non-Hodgkin lymphoma	umbralisib	Ukoniq	
Certain type of lung cancer	sotorasib†	Lumakras	
Certain type of leukemia*	avapritinib	Ayvakit	
Bile duct cancer	infigratinib†	Truseltiq	
Cell Cytoskeleton-modifying Agents			
Multiple myeloma	belantamab mafodotin-blmf	Blenrep	
DNA-damaging Agents			
Certain type of gastrointestinal cancers*	fam-trastuzumab deruxtecan-nxki	Enhertu	
Certain type of bladder cancer*	sacituzumab govitecan-hziy	Trodelvy	
Certain type of non-Hodgkin lymphoma	loncastuximab tesirine-lpyl	Zynlonta	
Multiple myeloma	melphalan flufenamide	Pepaxto	
Epigenome-modifying Agents			
Certain type of leukemia*	azacitidine	Onureg	
Hormones/Antihormones			
Certain type of prostate cancer	relugolix	Orgovyx	
Immunotherapeutics			
Certain types of skin and lung cancers*	cemiplimab-rwlc†	Libtayo	
Certain type of non-Hodgkin lymphoma	lisocabtagene maraleucel	Breyanzi	
Certain type of non-Hodgkin lymphoma*	axicabtagene ciloleucel	Yescarta	
Mesothelioma*	ipilimumab and nivolumab	Yervoy and Opdivo	
Neuroblastoma	naxitamab-gqgk	Danyelza	
Multiple myeloma	idecabtagene vicleucel	Abecma	
Certain type of endometrial cancer	dostarlimab-gxly†	Jemperli	
Gastric and gastroesophageal junction cancers*	nivolumab	Opdivo	
Certain type of breast cancer	margetuximab-cmkb	Margenza	
Certain types of breast, gastric, and gastroesophageal junction cancers*	pembrolizumab†	Keytruda	
Imaging Agents			
Prostate cancer	gallium 68 PSMA-11	Ga 68 PSMA-11	
Prostate cancer	piflufolastat F-18	Pylarify	
Certain type of neuroendocrine tumor	copper Cu 64 dotatate	Detectnet	
Companion Diagnostic Tests			
Certain type of lung cancer	N/A	Guardant360 CDx	
Certain types of breast, lung, ovarian, and prostate cancers	N/A	FoundationOne Liquid CDx	
Surgery Guiding Devices			
Osteoid osteoma in the extremities	N/A	Sonalleve MR-HIFU system	
Artificial intelligence-guided assessment for liver cancer	N/A	Hepatica	

*New cancer type approved 2020-2021
†Requires a companion diagnostic

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. Examples of these disparities include:

33% less likely	African American patients with non–small cell lung cancer were **33 percent less likely to receive surgery** for stage I-II disease compared to whites (402).
13% less likely	Patients with advanced colorectal or ovarian cancer who were uninsured or insured with Medicare, Medicaid, or other nonprivate insurance were **13 percent less likely to undergo surgery** when compared to patients who had private insurance (403).
Almost **DOUBLE**	During 2000-2016, the **time from cancer diagnosis to treatment was almost double** for poor Hispanics with colorectal cancer compared to non-Hispanic whites with similar socioeconomic status (404).
30% higher	Patients living in areas with a higher percent of high school graduates between January 1, 2013 and December 31, 2016, had **30 percent higher chances of receiving immunotherapy** for the treatment of aggressive skin cancer (405).
TWICE as likely	**Delaying cancer treatment was twice as likely** among cancer survivors living below the U.S. poverty guidelines compared to those earning the U.S. average household income (406).

Treating a Rare Bone Tumor with an Innovative Noninvasive Procedure

Osteoid osteoma is a benign, rare bone tumor, which commonly occurs in children and young adults (415). The most significant symptom of osteoid osteoma is pain. Current standard of care is removal of the tumor either by surgery or by computed tomography-guided radiotherapy (see sidebar **Using Radiation in Cancer Treatment**, p. 88). In November 2020, FDA approved Sonalleve Magnetic Resonance-guided High Intensity Focused Ultrasound (MR-HIFU) system, an innovative device that altogether eliminates the need for a scalpel or needle to treat osteoid osteomas. Instead, the device delivers focused ultrasound energy inside a lesion in a precise and controlled manner using an external applicator. In a clinical study, eight of the nine patients showed long-term relief from pain within four weeks of treatment and did not need any pain medication (416). The remarkable benefit of a noninvasive procedure for patients with osteoid osteomas, like **Niyati Shah** (see p. 84), highlights how innovative technologies are transforming the lives of patients, including those with rare tumor types.

Using Artificial Intelligence for Precision in Surgical Oncology

Rapid progress in the fields of artificial intelligence (AI) and machine learning (ML) is transforming the landscape of cancer research and care (see **Looking to the Future**, p. 130) (417). During the 12-month span covered in this report, FDA has authorized marketing of Hepatica, an AI-driven software that helps clinicians in making informed decisions before surgical removal of liver cancer. Hepatica uses noninvasive magnetic resonance imaging to provide an assessment of liver health. This assessment is based on dividing the liver into small segments digitally, combining these digital segments of liver with information obtained from biomarkers that detect

THE HONORABLE

Gus Bilirakis

U.S. Representative for Florida's 12th District

"As we celebrate the 50th anniversary of the National Cancer Act, it is important to reflect upon the substantial progress that has been made in the fight against cancer. While too many of our friends, family, and neighbors continue to battle cancer, we have made tremendous strides in developing more effective treatments and are seeing dramatically improved patient outcomes. With a better understanding of how different cancers develop, progress, and respond to targeted therapies, we now have realistic hope for an eventual cure on the horizon. I will continue to support federal investment in the groundbreaking research that will help us realize this goal and turn the dream into reality."

liver inflammation, and using an integrated AI algorithm to provide an evaluation of liver health. Using AI to delineate the size and health of liver takes 20 fewer minutes per patient compared to the traditional evaluation by a radiologist, thus saving valuable preoperative time. Initial results from a study involving 143 patients with liver cancer, who were surgical candidates, showed that Hepatica effectively identified patients at risk of poor outcomes from surgery and a longer hospital stay, thus preventing unnecessary surgical procedures (418). More than 42,000 new diagnoses of, and more than 30,000 deaths from, liver cancer are estimated in 2021 in the United States (3). Information gleaned from Hepatica can inform clinicians to better assess whether a patient is a good candidate for surgery and will benefit from it to treat liver cancer. Knowing precisely which parts of the liver need removing will also guide surgeons to avoid unnecessary removal of healthy tissue.

Researchers are also developing AI-based tools to ensure that all of the tumor tissue is removed during surgery. As an example, scientists have created a new microscope that can rapidly visualize relatively thick pieces of tissue with cellular resolution, allowing for inspection of margins between healthy tissue and the tumor within minutes of surgical removal. The microscope uses an AI program to optimize the collection and analysis of tissue images during surgery. As a result, it takes less time for surgeons to detect any leftover tumor tissue during the procedure, while potentially increasing the accuracy of detection (419). This approach can be further enhanced by molecular imaging approaches, which are currently being developed.

THE IMPACT OF COVID-19 ON CANCER TREATMENT

The COVID-19 pandemic has had a negative impact on cancer care at multiple levels. Limited mobility from the unprecedented public health challenge posed by the pandemic and the nationwide lockdown policies to contain the spread of the disease has resulted in interruptions in all pillars of the cancer treatment paradigm:

A **39 percent decrease was seen in surgeries for colon cancer** in April 2020—the peak of the pandemic—compared to prepandemic levels (409).

67 percent of patients experienced a **delay in receiving chemotherapy** during the height of the pandemic compared to prepandemic levels (410).

66 percent of radiation oncologists surveyed **reported interruptions in radiotherapy** for existing cancer patients due to the pandemic (411).

A **60 percent decrease** was observed in the **number of new oncology clinical trials** launched during the five months at the height of the pandemic (January 2020 to May 2020) compared to a prepandemic period (October 2018 to May 2019) (68).

More than 26 percent of lung cancer patients who were being actively treated before the pandemic with chemotherapy, molecularly targeted therapy, or immunotherapy **experienced a change in either treatment dosing**, i.e., how much anticancer therapeutic was administered, **or schedule**, i.e., how frequently the treatment was given (412).

Continued on page 86 ▸

NIYATI SHAH AGE 17 | Nokesville, Virginia

Lifeguarding, Spending Time with Friends, and Preparing for College, Thanks to Noninvasive Treatment

A Message from Bhavesh and Nita Shah, Niyati's Parents

When Niyati was 10 years old, she started coming home every night after swim practice with excruciating pain in her shins. For a long time, the doctors were not able to identify the cause of the pain. Finally, an MRI test performed with a contrast dye led to her diagnosis of osteoid osteoma, a very rare type of tumor. She took part in a clinical trial that was testing a noninvasive procedure known as Magnetic Resonance-guided High Intensity Focused Ultrasound (MR-HIFU) for the treatment of osteoid osteomas. Since the treatment, her pain is completely gone; she is tumor free and living a normal, healthy life.

Our daughter Niyati has been a swimmer since she was a child. When she was about six, she joined a swim team and at the age of 10, she started experiencing severe pain in her shin every night after her practice. Initially, her pediatrician attributed it to "growing pains" and prescribed ibuprofen. Unfortunately, the pain kept coming back, especially in the evening hours. There was a pattern to the pain. We followed up with X-rays and several rounds of physical therapy, but nothing seemed to help. The pain just would not go away. Niyati started missing school because she couldn't sleep at nights. For us as parents, it was heartbreaking. We had many sleepless nights just watching her cry in pain. We just couldn't figure it out. Finally, her doctor recommended an MRI with a contrast dye. She also recommended imaging her entire leg, even though the pain was in her shin. That is how we found out that there was a tumor in her femur. Prior imaging had missed it because X-rays were done below the knee where she was experiencing the pain.

Our pediatrician put us in touch with a physician at the Children's National Hospital, who diagnosed Niyati with osteoid osteoma. He told us that this was a rare tumor that causes pain, which can worsen at night. He also suggested that we enroll Niyati into a clinical trial for a noninvasive procedure called MR-HIFU. The procedure uses magnetic resonance imaging to focus a high-intensity ultrasound beam into tumors. The beam heats the tumors and destroys them. While conventional surgery was a backup option, we were keen on this new treatment for Niyati, given the noninvasive nature of the procedure. Her physician explained that even if MR-HIFU did not work, there would be no harm done.

Before the procedure, Niyati had to undergo tests to make sure that the tumor was not too close to her nerves to avoid damage from MR-HIFU. On the day of her procedure, we were accompanied by a large team of pediatric doctors, nurses, and other staff, all of whom took great care of Niyati throughout the entire process. We were just so blessed to have such a caring team of health care providers who made our daughter feel like she was at Disney. They were so welcoming that she enjoyed the whole process. We were elated that the procedure worked. Since her treatment, Niyati has had absolutely no pain. She is tumor free and living a normal life as a teenager. She is a completely new person.

We feel very blessed that there was a cure for Niyati's disease because of the technological advances in cancer treatment. The federal government needs to invest in research and development to find cures so that patients with cancer can live a normal life and not be in constant fear. At the same time, our government and the research institutions need to raise public awareness of the research and scientific breakthroughs that are happening in the field. It is our ardent request to the Congress that they prioritize funding to the NIH and to all other research institutions that are working on the many aspects of human biology so that no human being is lost to cancer. Niyati would not be where she is today without funding for medical research.

Niyati would not be where she is today without funding for medical research.

USING SURGERY IN CANCER CARE

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

- **Surgery to diagnose cancer:** In some cases, surgery is performed to obtain a tumor sample, or biopsy, for diagnosing cancer.
- **Surgery to stage cancer:** Some cancer patients require surgery to determine how far the cancer has spread from the site of origin. This information is vital for establishing the best treatment plan for a patient.
- **Surgery to cure cancer:** If cancer is confined to one area of the body, sometimes surgery can be performed to remove the entire tumor.
- **Surgery to debulk a cancer:** If a tumor is extremely large and/or located very close to important organs or tissues, surgery may be recommended to remove only part of the tumor.
- **Surgery to ease problems caused by a cancer:** For patients with advanced cancer, surgery can sometimes be performed palliatively to remove tumors that are causing pain, pressure, or blockages.

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 healthy tissue, and maybe some nearby lymph nodes.

Minimally invasive surgery is when a surgeon makes a few small cuts instead of one or more large ones. A long, thin tube with a tiny camera is inserted into one of the small cuts, allowing the surgeon to see what is happening, and special surgery tools are inserted through the other small cuts to remove the tumor and some healthy tissue surrounding the tumor.

Improving Surgical Outcomes for Patients with Early-stage Cervical Cancer

Roughly 44 percent of women with cervical cancer are diagnosed at an early stage, when tumors are small and cancer has not spread beyond the cervix (3). The most common treatment for women diagnosed with early-stage cervical cancer is removal of the uterus either by open surgery or using minimally invasive surgical procedures. In 2018, results from a clinical trial showed that traditional open surgery for early-stage cervical cancer was superior to minimally invasive surgery (420). Researchers found that even though minimally invasive surgery caused less blood loss during the procedure, shortened length of hospital stay, and resulted in less complication after surgery, patients who underwent traditional, open surgery lived longer free of disease and their overall survival increased compared to those treated with minimally invasive surgery (see **Table 6**, p. 87). These data are helping both surgeons and patients to make informed decisions to opt for traditional surgery. According to a new report, the use of minimally invasive surgery has decreased from 58 percent to 43 percent in the 18 months since the publication of the aforementioned clinical trial (421). These evidence-based changes in clinical practice also underscore the iterative nature of the medical research cycle to improve outcomes for cancer patients as new evidence accumulates (see **Figure 16**, p. 73).

IMPROVEMENTS IN RADIATION-BASED APPROACHES FOR CANCER CARE

Radiotherapy uses high energy rays or particles to control the growth of and/or eradicate cancer cells by damaging their DNA. Discovery of X-rays in 1895 allowed visualization of internal organs at low doses. A year later, the effective use of X-rays at high doses to treat a breast cancer patient firmly established radiotherapy as the second pillar of cancer treatment (398) (see **Figure 19**, p. 80). Today, about 50 percent of all cancer patients in the United States receive radiotherapy as part of their treatment regimens. The number of cancer survivors who have received radiotherapy is projected to increase from 3.38 million in 2020 to 4.17 million in 2030 (422).

TABLE 6

COMMONLY USED TERMS AND BENCHMARKS IN CLINICAL STUDIES

Term/Benchmark	Definition
Adjuvant therapy	An anticancer therapy that is administered after surgery to eradicate as many residual cancer cells as possible.
Complete response	Cancer that is undetectable by any available methods.
Duration of response	Time from documentation of disease response to disease progression.
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 – PR) and/or disappears (Complete response–CR) 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 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.
Systemic therapy	Any type of cancer treatment that targets the entire body, for example, chemotherapy.

There are many types and uses of radiotherapy (see sidebar on **Using Radiation in Cancer Treatment**, p. 88). However, it is important to note that radiotherapy may also have harmful side effects, partly because of the radiation-induced damage to healthy organs surrounding the tumor tissue. Researchers are continuously working on making radiotherapy safer and more effective and also designing novel radiotherapeutics (alone or in combination) to target more cancer types and benefit more patients. One area of rapid development is the use of AI to enhance radiotherapy and the integration of such improved approaches into clinical practice to increase efficacy and reduce toxicity from these treatments (423).

Imaging Prostate Cancer More Clearly

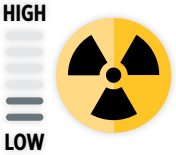
Prostate cancer is the most common type of cancer in men in the United States, with more than two men estimated to be diagnosed every minute in 2021 (3). It is also the second deadliest cancer in men behind only lung cancer. Prostate cancer that is confined to the prostate is usually treated with surgery or radiation therapy. The more precise a patient's diagnosis, the easier it is for a health care provider to tailor the treatment to ensure that it is as effective and safe as possible. Among the tools physicians use to make cancer diagnoses is positron emission tomography–computed tomography (PET–CT or PET), a form of imaging that can help physicians precisely locate the position of a patient's cancer within his body and determine the extent to which the cancer may have spread.

Before a PET scan, patients are injected with a radioactive imaging agent. The PET scan detects where in the body the radioactive agent accumulates. In December 2020, FDA approved the agent Gallium-68 PSMA-11 (Ga 68 PSMA-11) as the first molecule that enables the PET imaging of recurrent prostate cancer in men by binding to the prostate-specific membrane antigen (PSMA). PSMA is a protein that is present in abundance on the surface of more than 90 percent of primary and metastatic prostate cancer cells. Ga 68 PSMA-11 contains a short peptide sequence that binds to PSMA and is also attached to Ga 68 radionuclide to enable imaging. When the short peptide binds to PSMA, radiation emitting from radionuclide can be imaged using PET. Clinicians are able to use this information to decide which patient should receive surgery and spare others from unnecessary surgical procedures.

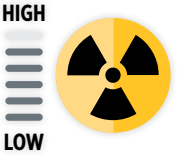
Findings from the two clinical trials that FDA used to approve Ga 68 PSMA-11 indicate that detection of prostate cancers using this approach may help physicians make the best treatment decisions for patients. In one study, prostate cancer patients who were considered at high risk of metastasis, as confirmed by biopsy, underwent PET imaging with Ga 68 PSMA-11 prior to surgical removal of the prostate gland and nearby lymph nodes present in the pelvis. Following surgery, pathological analysis of

USING RADIATION IN CANCER TREATMENT

There are two major uses of ionizing radiation in the diagnosis and treatment of cancer:



Radiology largely uses low-energy radiation to image tissues to diagnose disease, e.g., Gallium 68 PSMA-11 (Ga 68 PSMA-11) and piflufolastat F 18 (Pylarify) radiopharmaceuticals that have been recently approved by FDA to detect metastatic prostate cancer lesions.



Radiotherapy, or radiation therapy, uses high-energy radiation to control and eradicate cancer.

Radiotherapy

- 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 eliminate cancer.
- Radiotherapy works primarily by damaging DNA, leading to cancer cell death with relative sparing of normal tissues, a feat achieved by using sophisticated approaches, such as computer analytic programs that optimize the delivery of the radiation to the tumor while minimizing exposure of normal tissues.

Uses of Radiotherapy

Curative radiotherapy seeks to eliminate cancers, particularly small and locally advanced cancers; it is often used in combination with systemic therapy.

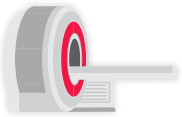
Neoadjuvant radiotherapy is used to shrink a tumor so that it can be subsequently treated by a different method such as surgery.

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

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

Types of Radiotherapy

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



- Conventional (2-D) external beam radiation therapy delivers a high-energy X-ray beam from one or more directions. Imaging of the treatment area is typically performed using low-energy diagnostic X-rays. It is primarily used in settings where high precision is not required, such as in the treatment of bone metastases.
- 3-D conformational radiotherapy (3DCRT) uses specialized imaging, usually computed tomography (CT) and/or magnetic resonance imaging (MRI) and planning software to deliver high-energy X-rays via multiple beams that more precisely target the shape and size of the tumor.
- Intensity-modulated radiotherapy (IMRT) is a refinement of 3DCRT that more precisely focuses and shapes the radiation by dividing each beam into many "beamlets," each of which can have a different intensity.
- Intraoperative radiation therapy uses electron beam (superficial) radiation directly on tumors that have been exposed during surgical procedures.
- Stereotactic radiotherapy is used in both stereotactic surgery (SRS) and stereotactic body radiotherapy (SBRT). It uses typically more than eight beams with a highly sophisticated imaging system to direct radiation to very well-defined smaller tumors. Usually, SRS is used to treat tumors of the brain and central nervous system, whereas SBRT can be used on small tumors within larger organs of the body.

Particle therapy refers to protons or carbon ions rather than X-rays as the source of energy. In contrast to X-rays that cause damage to the noncancerous tissues through which they pass, these heavier particles deposit most of their energy in the target. In this manner, particle therapy can deliver higher doses with less damage to surrounding tissue. 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 places small radioactive sources in or next to the tumor either temporarily or permanently.

Radioisotope therapy involves systemic ingestion or infusion of radioisotopes, for example, iodine-131 to treat thyroid cancer or lutetium Lu 177 dotatate (Lutathera) to treat gastroenteropancreatic neuroendocrine tumors.

the removed lesions confirmed that patients who had positive readings on Ga 68 PSMA-11 PET in the pelvic lymph nodes were likely to have metastatic prostate cancer.

Prostate specific antigen (PSA) is a secreted biochemical marker that is used to screen individuals for prostate cancer. In prostate cancer patients who have received treatment, PSA is used for predicting recurrence of the disease. In another clinical trial 635 patients who had rising serum PSA levels after initial prostate cancer treatment with surgery or radiotherapy, underwent a single Ga 68 PSMA-11 PET scan. Seventy-four percent of patients had at least one positive lesion detected by Ga 68 PSMA-11. Among patients with positive PET readings, prostate cancer recurrence or metastasis was definitively confirmed in more than 90 percent of cases using pathological tests (424–428). Thus, Ga 68 PSMA-11 PET can accurately detect sites of recurrent or metastatic prostate cancer, thereby providing important information that may impact clinical care.

In May 2021, FDA approved another radioactive agent, piflufolastat F 18 (Pylarify), that also targets PSMA to detect prostate cancer lesions that can be imaged by PET. Like Ga 68 PSMA-11, piflufolastat F 18 is a short peptide attached to a radionuclide and is administered in the form of an intravenous injection. Knowledge gleaned from the procedure can be used to make individualized informed decisions about the course of treatment.

FDA approval was based on results from two clinical trials: the first in which patients who already had confirmed prostate cancer as detected by biopsy were subjected to piflufolastat F 18 injection followed by PET imaging, and the second in which patients who had elevated levels of PSA following initial treatment with surgery or radiation were given the piflufolastat F 18 injection followed by PET imaging. In both trials, the piflufolastat F 18-based PET imaging detected the presence of metastatic prostate cancer with high accuracy.

Together, the approvals of Ga 68 PSMA-11 and piflufolastat F 18 are anticipated to help certain patients with prostate cancer avoid unnecessary surgery and undergo a treatment regimen that is tailored for their specific situation.

Detecting Neuroendocrine Tumors with High Accuracy

Neuroendocrine tumors (NET) are cancers that arise in a type of cells in the body, called neuroendocrine cells , that have properties of both nerve and hormone-producing cells and perform specific functions, such as regulating blood flow (429). NET are considered rare, with an estimated 12,000 people in the United States diagnosed each year (3). Because neuroendocrine cells are located throughout the body and perform different functions, the outcome and survival rates for patients vary depending on the type of NET, the tissue of origin, and the feasibility of surgical removal.

In September 2020, FDA approved copper Cu 64 dotatate (Detectnet), to detect certain types of NET. Copper Cu 64 dotatate binds to somatostatin receptors, proteins found in high abundance on the surface of malignant neuroendocrine cells. Copper 64 (Cu 64) is a positron emitting radionuclide, allowing PET imaging of NET. Approval was based on findings from two clinical studies. One study prospectively evaluated 63 participants, of which 42 patients had known or suspected NET as determined by histology, conventional imaging, and/or clinical evaluation. Copper Cu 64 dotatate detected NETs with 91 percent accuracy, as evaluated by three independent oncologists. The second study was a retrospective analysis of published data collected from 112 patients with known history of NET and showed similar performance by copper Cu 64 dotatate. The clinical benefit offered by high accuracy of detecting NET using copper Cu 64 dotatate will guide clinicians in developing a personalized treatment approach for NET patients.

ADVANCES IN TREATMENT WITH CYTOTOXIC CHEMOTHERAPY

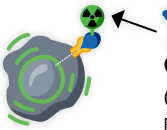
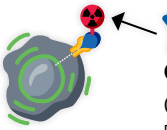
Cytotoxic chemotherapy—use of chemicals to kill cancer cells—remains the backbone of cancer treatment for many patients. First introduced as a pillar of cancer treatment in the early to mid-20th century, use of cytotoxic chemotherapy is continually evolving to minimize its potential harms to cancer patients, while maximizing its benefits (399).

Reducing the Risk of Blood Cancer Recurrence

Acute myeloid leukemia (AML) is a type of blood cancer. It is estimated to be diagnosed in more than 20,000 Americans in 2021 (3). Patients with AML undergo intensive first-line chemotherapy to eradicate cancer cells. After the initial chemotherapy, stem cell transplantation is often required to replenish blood-forming cells. Some AML patients need additional intravenous administration of chemotherapeutic agents to prevent recurrence of the disease. Both procedures require a hospital visit and/or stay (431).

Researchers are continuously improving the formulation of cytotoxic chemotherapeutics to make them more effective at lower doses, as well as more convenient to administer. In September 2020, FDA approved a new formulation of azacitidine (Onureg) as a maintenance treatment for adults with newly diagnosed AML who had achieved complete remission after intensive chemotherapy. Azacitidine is a routinely used chemotherapeutic drug that is typically injected under the skin or into a vein by a medical professional in a medical facility. The newly approved formulation is in a tablet form that allows for convenient dosing and permits easier delivery of azacitidine as a maintenance therapeutic. The clinical trial evaluating safety and efficacy of the new formulation found that once daily oral administration of azacitidine increased the life spans of AML patients by nearly one year compared to those patients who only received placebo (432). The drug also reduced the risk of relapse by 35 percent compared to a placebo without compromising health-related quality of life. The approved formulation, which is a result of more than a decade of research and 13 preclinical and clinical studies, makes azacitidine the first oral chemotherapeutic for maintenance therapy in AML

Theragnostics, or **theranostics**, is a cancer treatment strategy in which **cancer is visualized by PET/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, often labeled with more potent radioactive compounds, are then used to kill cancer cells.

Cancer Type	Diagnostic Agent	Therapeutic Agent
Neuroendocrine Tumors	 FDA APPROVED **Gallium Ga 68 dotatate** (Netspot) FDA-approved in 2016	 FDA APPROVED **Lutetium Lu 177 dotatate** (Lutathera) FDA-approved in 2018
Prostate Cancer	 FDA APPROVED **Gallium 68 PSMA-11** (Ga 68 PSMA-11) FDA-approved in 2020	 **Lutetium 177 PSMA-617** (Adacap) In phase III clinical trial

In addition to the examples above, there are several ongoing clinical studies investigating the potential of many radiopharmaceuticals in diagnosis and treatment of many cancer types (430).

patients who are in complete remission (433). This approval will especially benefit those AML patients who are not able to complete intensive curative therapy, such as stem cell transplantation.

Effectively Delivering Cytotoxic Drugs to Kill Multiple Myeloma Cells

Multiple myeloma is one of the most diagnosed blood cancers in the United States (3). Over the last two decades, there has been unprecedented progress toward developing new precision medicine-based treatments for multiple myeloma (see sidebar on **Two Decades of Progress Against Multiple Myeloma**, p. 91). Despite the advances, many patients develop resistance to treatment over time and then the disease returns.

Recurring or relapsed multiple myeloma is particularly challenging to treat because patients with recurring or relapsed multiple myeloma often develop resistance to available treatments. In February 2021, FDA approved melphalan flufenamide (Pepaxto), a first-in-class hybrid drug. Melphalan flufenamide combines a potent cytotoxic agent with a peptide that helps rapid uptake of the drug by myeloma cells and quickly releases the cytotoxic agent once inside the cells (435). The high concentration of the above cytotoxic drug kills multiple myeloma cells, and this approach has been effective in treating patients who have developed resistance to other types of treatment. Melphalan flufenamide was approved in combination with dexamethasone, a commonly used steroid with anti-inflammatory and immunosuppressive effects, for adult patients with relapsed or refractory multiple myeloma who have received at least four prior treatments and whose disease no longer responds to at least one proteasome inhibitor, one immunomodulatory agent, or one CD-38 directed monoclonal antibody. The approval was based on results from an ongoing clinical trial in which nearly 30 percent of the participating multiple myeloma patients, who had developed resistance to other treatments, responded to melphalan flufenamide and had an overall survival of nearly a year (436). A continued evaluation of patients' response to the drug will be important to further improve overall outcome.

ADVANCES IN TREATMENT WITH MOLECULARLY TARGETED THERAPY

Advances in precision medicine, fueled by discovery science, are providing a deeper understanding of the numerous genetic mutations that drive cancer development and are thus offering clinicians a new arsenal of molecularly targeted therapeutics against cancer. As a result, cancer patients now have many treatment options available that are specific to the genetic changes driving their cancer or based on the characteristics of their cancer type. Importantly, therapeutics directed to the molecules influencing cancer cell multiplication and survival target the cells within a tumor more precisely than cytotoxic chemotherapeutics which target all rapidly dividing cells, thereby limiting damage to healthy tissues. The greater precision of molecularly targeted therapeutics tends to make them more effective and less toxic than cytotoxic chemotherapeutics. 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.

Between August 1, 2020 and July 31, 2021—the 12-month period covered in this report—FDA has approved 10 new anticancer therapeutics that are directed against particular molecules or genetic mutations (see **Table 5**, p. 81). A

TWO DECADES OF PROGRESS AGAINST MULTIPLE MYELOMA

Most Recent Stats At-A-Glance

2021 U.S. ESTIMATES

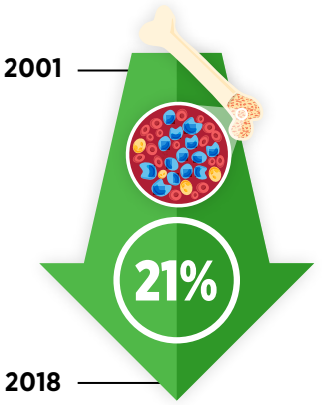
34,920 New Cases

12,410 Deaths

FDA APPROVED THERAPIES
(AUG 1, 2020-JUL 31, 2021)

- 1 Immunotherapy
- 1 Molecularly Targeted Therapy
- 1 Chemotherapy

Percent Decrease in Multiple Myeloma Deaths



FDA Approved Drugs to Treat Multiple Myeloma

Multiple myeloma causes abnormal growth of plasma cells, which are blood cells that make antibodies to protect against infections (435). In 2021, nearly 35,000 Americans are expected to be diagnosed with multiple myeloma, and more than 12,000 are expected to die from it (419). Thanks to the unprecedented progress toward developing new precision-medicine-based treatments, mortality rates of multiple myeloma have declined 21 percent in the past two decades (4). In 2001, there were only six FDA-approved drugs—all cytotoxic chemotherapeutics—to treat multiple myeloma patients. Today, clinicians have 20 FDA-approved drugs—of which 13 are molecularly targeted therapeutics or immunotherapeutics—at their disposal to treat multiple myeloma. In 2021, FDA approved a revolutionary new immunotherapeutic, the first BCMA-targeted CAR T-cell therapy, to treat patients with multiple myeloma (see **Engineering Immune Cells to Eliminate Cancer**, p. 115).

significant breakthrough in molecularly targeted therapeutics covered in this report is the FDA approval of sotorasib (Lumakras) for the treatment of certain patients with lung cancer. Sotorasib is a molecularly targeted therapeutic specifically developed to target an altered from of KRAS that is produced by the G12C mutation, one of the most common non–small cell lung cancer-associated mutations and previously considered an undruggable target (see section on **New Wave of Innovation to Aim at Cancer's Most Intractable Targets**, p. 133).

Additionally, FDA also expanded the use of five previously approved molecularly targeted therapeutics to treat new types of cancer. These expansions included treatment of anaplastic large-cell lymphoma (ALCL) patients with crizotinib (Xalkori), a molecularly targeted therapeutic first approved to treat lung cancer with alterations in the ALK gene. The experimental use of crizotinib for the treatment of ALCL was first highlighted in the *AACR Cancer Progress Report 2014* through the experience of Zachary (Zach) Witt, a nine-year-old at the time, who participated in the clinical trial testing crizotinib (129). The inspiring journey of **Zach** (see p. 104), now a 16-year-old high school student, underscores how discovery science drives clinical breakthroughs to save and improve the lives of cancer patients.

A New Breakthrough in Treating Lung Cancer

One of the most significant advances in cancer precision medicine in the 12 months covered in this report was the FDA approval of sotorasib. Sotorasib is the first ever molecularly targeted therapeutic designed to target the KRAS G12C mutation, one of the most frequent genetic alterations found in NSCLC patients. The FDA also approved a companion diagnostic (see sidebar on **Companion Diagnostics**, p. 92), called the Guardant Health-developed Guardant360 CDx test, to help identify patients with NSCLC carrying the KRAS G12C mutation.

Remarkable progress has been made toward prevention and treatment of lung cancer in the past five decades (see **Landmark Discoveries Fueling Advances in Lung Cancer Diagnosis and Treatment**, p. 14). Yet lung cancer remains the third most diagnosed and the deadliest cancer in the United States, with 27 new diagnoses and 15 deaths estimated every hour in 2021 (3). The NSCLC subtype of lung cancer constitutes about 84 percent

COMPANION DIAGNOSTICS

The use of anticancer therapeutics that target defined molecular abnormalities present in the cancer requires reliable detection of these cancer-specific characteristics. The FDA typically approves specialized tests, called companion diagnostics, alongside the approvals of molecularly targeted therapeutics or immunotherapeutics.

Companion diagnostics:

- Accurately match patients with a specific therapy

- Are stringently tested for accuracy, sensitivity, and fidelity

- Are regulated by the U.S. Food and Drug Administration

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

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

Between August 1, 2020 and July 31, 2021—the period covered by this report—FDA has approved the **first comprehensive pan-tumor liquid biopsy test**, called FoundationOne, for certain patients with advanced cancers, and a **second liquid biopsy test**, called Guardant 360, to inform treatment options for certain patients with lung cancer (133).

of all lung cancers, and approximately 25 percent of NSCLC patients carry mutations in KRAS, an essential protein needed for growth and survival of normal lung cells (437). For early-stage NSCLC, surgery is the standard treatment, sometimes with chemotherapy, alone or in combination with radiation therapy. Advanced-stage NSCLC is usually treated with chemotherapy and/or immunotherapy. Unfortunately, NSCLC patients who harbor KRAS mutations develop resistance to other types of treatments, and only 25 percent of these patients live five years or more after diagnosis (see sidebar on **The Challenge of Treatment Resistance**, p. 93) (438).

The FDA approved sotorasib (Lumakras) for adult NSCLC patients with locally advanced or metastatic disease, whose tumors harbor the KRAS G12C mutation, a genetic alteration more frequently found in former or current smokers (439). The approval of sotorasib was based on a phase II clinical trial (440). Treatment with sotorasib shrank tumors in over 37 percent of NSCLC patients who had responded poorly to previous treatment with either chemotherapy or immunotherapy. Importantly, responses lasted more than 11 months, and progression-free survival (see **Table 6**, p. 87), a measure of how long cancer is held in check, was almost seven months. Even with relatively modest benefits, these responses were roughly two times higher compared to historical results achieved through standard chemotherapy regimens and mark a significant advance for the treatment of patients with KRAS-mutated lung cancer, for whom there are no good options after initial treatment. Developing effective therapeutics that target KRAS has been a daunting challenge and discoveries over the past five decades have fueled the development of sotorasib (**Figure 20**, p. 96). Approval of sotorasib and other KRAS inhibitors that are progressing from the bench to the clinic not only brings hope for NSCLC patients, such as **Steve Castellaw** (see p. 94), but it also holds future promise for treating other KRAS-mutated malignancies that include pancreatic and colorectal cancers.

Targeting Protein Kinases for Treatment of Solid Tumors

In addition to the landmark approval of sotorasib, in the 12 months covered in this report FDA also approved three new molecularly targeted therapeutics—amivantamab-vmjw (Rybrevant), pralsetinib (Gavreto), and tepotinib (Tempetko)—for the treatment of lung cancers that harbor certain alterations in the EGFR, RET, or MET genes, respectively. EGFR, RET, and MET belong to a family of proteins called receptor tyrosine kinases which are located on the surface of cancer cells and play a critical role in the development and progression of many cancer types.

In May 2021, FDA approved amivantamab-vmjw for adult patients with locally advanced or metastatic NSCLC, whose cancer continued to progress after chemotherapy and who have certain alterations in the EGFR gene (insertion mutations in exon 20). The FDA also approved the Guardant360 CDx liquid biopsy test as a companion diagnostic for amivantamab-vmjw to identify patients who have the exon 20 insertion mutant forms of the EGFR gene.

Patients with NSCLC whose tumors harbor insertion mutations in the region exon 20 of the EGFR gene do not respond well to EGFR-targeted therapeutics, such as osimertinib, and generally have poor prognosis (441). Amivantamab-vmjw is a first-in-class bispecific antibody approved to treat aggressive forms of NSCLC. Unlike molecularly targeted therapeutics such as osimertinib that work by inhibiting the function of EGFR, amivantamab-vmjw binds to two different receptor tyrosine kinase proteins—EGFR and MET—present on the surface of lung cancer cells and disrupts EGFR and MET functions through blocking ligand binding and/or degradation of EGFR and MET proteins. The presence of EGFR and MET on the surface of tumor cells also allows for targeting of these cells for destruction through antibody-dependent cellular cytotoxicity (ADCC) (442). The FDA decision was based on results from a phase I clinical trial showing that amivantamab-vmjw significantly reduced tumors in 40 percent of the patients. Moreover, these responses lasted at least six months in the majority of patients who were sensitive to amivantamab-vmjw. These encouraging results, and the approval of amivantamab-vmjw, provide a new treatment option for patients with a debilitating form of lung cancer.

In February 2021, FDA approved the targeted therapy tepotinib for treating certain patients with NSCLC. Tepotinib targets an aberrant form of the protein MET, which arises from a genetic alteration known as exon 14 skipping in the MET gene found in approximately 3-4 percent of NSCLC patients (443). This alteration is observed in many cancer types (such as lung, thyroid, colorectal, ovarian, breast, and pancreatic cancer) and leads to the overactivation of the MET protein, which causes uncontrolled growth of cancer cells (444). NSCLC patients with MET alterations have limited treatment options and a poor clinical outcome. The FDA approved tepotinib for NSCLC patients with advanced or metastatic disease harboring the exon 14 skipping alterations in MET based on results from a phase II clinical trial (445). More than 40 percent of NSCLC patients with advanced or metastatic disease who received tepotinib had shrinkage of their tumors and had sustained response to the treatment for nearly one year. Continued follow-up of NSCLC patients treated with tepotinib will be necessary to establish long-term clinical benefit.

Pralsetinib is designed to treat patients with lung cancer who harbor certain genetic alterations in RET, a protein necessary for growth of normal lung cells. While the activity of RET protein is tightly regulated in normal cells, various mutant forms of the RET gene produce hyperactive proteins in cancer cells and result in uncontrolled cell growth. Mutant RET forms found in lung and other cancers include chromosomal translocations that result in fusion genes, missense mutations, and insertions and deletions (see sidebar on **Genetic Mutations**, p. 30) (446). Cancer patients with altered RET proteins (such as lung and thyroid cancer patients) have limited treatment options and poor survival. In September 2020, FDA approved the molecularly targeted therapeutic pralsetinib for the treatment of NSCLC patients harboring alterations in RET proteins. Findings from a phase I/II basket clinical trial (see sidebar on **Types of Clinical Trials**, p. 75) that informed the FDA decision showed a significant reduction in tumor size in almost 60 percent of NSCLC patients treated with pralsetinib and complete responses in nearly six percent of the treated patients (447).

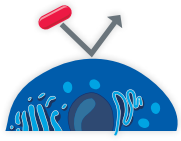
Continued on page 96 ▸

THE CHALLENGE OF TREATMENT RESISTANCE

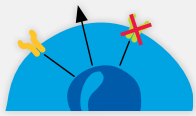
Diversity, or heterogeneity, among cancer cells within and between tumors is a major cause of treatment resistance. Some examples of heterogeneity are as follows:

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

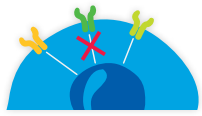
Some cancer cells in a tumor may have or may acquire mutations in the target of a given treatment that render the treatment ineffective.



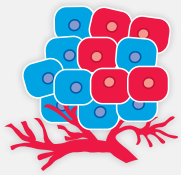
Some cancer cells in a tumor may have or may acquire molecular or cellular differences other than changes in the treatment target that render the treatment ineffective.



Redundancies among signaling networks fueling proliferation can enable cancer cells to become resistant to a treatment.



Differences in tumor microenvironment components can render a treatment ineffective.



STEVE CASTELLAW AGE 76 | Highlands, North Carolina

Back to the Golf Course and a Normal Lifestyle, Thanks to Sotorasib

About three and a half years ago I found a lump on the side of my head, which led to my diagnosis of stage IV lung cancer. It was a total shock. With the help of my wife, I was able to get an appointment at the MD Anderson Cancer Center within days of my diagnosis. After a few initial treatments that controlled the cancer temporarily, I participated in a clinical trial for a targeted therapeutic called sotorasib (Lumakras) and have been on this treatment for the past two years. My latest scans show that the treatment continues to be effective. I am back at the course playing golf, spending time with family, and living a normal day-to-day life.

My experience with cancer started about three and a half years ago when I was 72. The lady who trims my hair noticed a lump on the side of my head. I decided to get it checked out at my next physical examination with my GP. My doctor suggested an MRI after which I was rushed to a surgery and biopsy right away. The following day I received my diagnosis of stage IV lung cancer. The tumor was in my left lung and had metastasized to my right pelvis, the L1 and L2 vertebrae on my spine, and up to my skull. The news felt like someone hit me in the head with a baseball bat. I had been getting my regular physical examinations every 12 or 15 months for the last four decades and had never had any problems. This was a rude awakening.

My wife has been my biggest supporter throughout this experience. Right after my diagnosis she contacted a friend who is a doctor and who helped us get an appointment at the MD Anderson Cancer Center, which is where I am being treated.

My initial treatment was chemotherapy and even though it was quite effective at first, the cancer stopped responding after a while. After Thanksgiving in 2018, my oncologist switched my treatment to an immune checkpoint inhibitor. Like chemotherapy, the immunotherapy initially worked to control my cancer but then stopped. At this point I spoke with the physicians in the clinical trial department. They performed some tests and based on the findings I was selected to be a part of the clinical trial testing a molecularly targeted therapeutic called sotorasib. Since then, I have been receiving sotorasib for about two years and the treatment has been holding its course. I saw a big reduction in tumor size. Other than a light swelling of the ankles and some skin rash I have had no side effects. I travel to MD Anderson Cancer Center for my follow-up every three weeks and every 12 weeks I receive an MRI of my brain and a CT body scan. As of my last follow-up, everything is still looking good.

Compared to where I was five years ago, the only real difference is that I am five years older. Otherwise, I am still playing golf, doing my exercises, and living a normal lifestyle. My health care team at MD Anderson has been like my family through this entire experience and I can't thank them enough for their care and support.

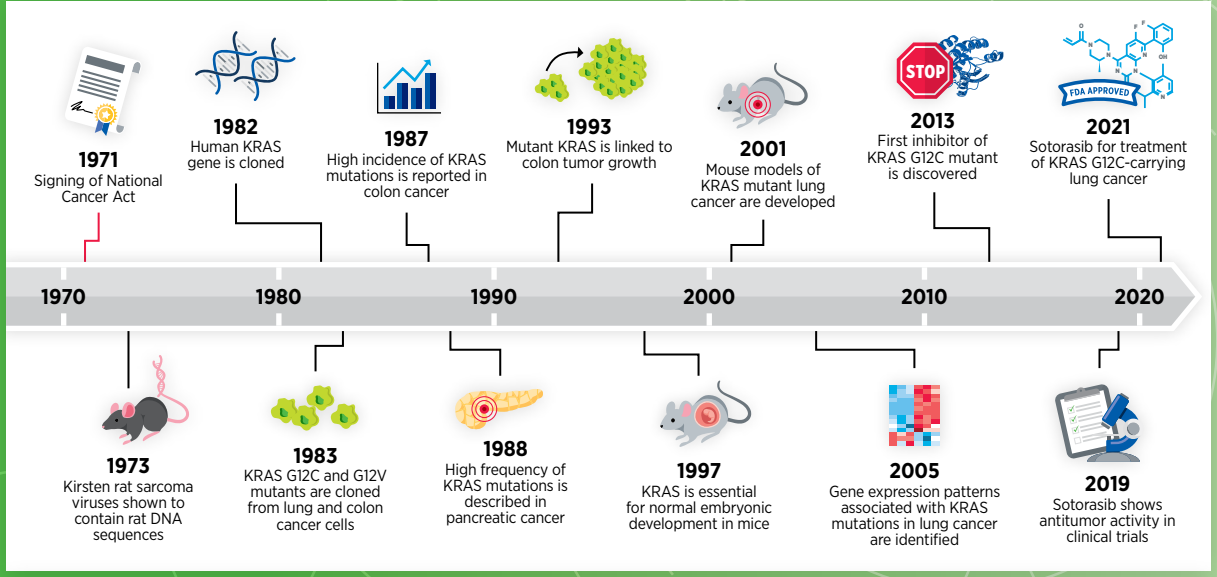
I tell anyone who wonders about the importance of cancer research to take a walk through the halls of the cancer center. You see patients from four or five years old to those in their eighties or nineties. Cancer knows no boundaries. It affects people of all ages, races, colors, and creeds. Only by funding cancer research can we keep moving forward against this devastating disease and bring hope to the many patients who need it the most.

Cancer knows no boundaries. It affects people of all ages, races, colors, and creeds. Only by funding cancer research can we keep moving forward against this devastating disease and bring hope to the many patients who need it the most.

FIGURE 20

NATIONAL CANCER ACT
50 YEARS
1971-2021

50 YEARS OF MILESTONES IN THE JOURNEY TO TARGET THE UNDRUGGABLE KRAS



Five decades of research led to the development and approval of sotorasib in May 2021. The relationship between RAS genes and lung cancer was first described in 1984, and subsequent discoveries led to the development of direct and indirect inhibitors of KRAS activity. The first clinical trials investigating the efficacy of indirect KRAS inhibitors were carried out in the early 2000s. Since then, many KRAS inhibitors have been developed and tested. Targeting KRAS with small molecular inhibitors has been particularly challenging because the protein was considered to lack an accessible or "druggable" pocket when present in its three-dimensional form in the cells. With the dawn of precision medicine and availability of deeper insights into the mutational landscape of lung cancer, a renewed enthusiasm and biological and clinical progress have led to the development of sotorasib (Lumakras), which was approved in May 2021 by FDA based on promising results from preclinical and clinical studies.

According to the most recent estimates, about 44,280 new cases of thyroid cancer will be diagnosed in the United States in 2021; one third of these cases will be among AYA (ages 15 to 39) (3). Thyroid cancer has many subtypes, the most common of which is called papillary thyroid cancer. Papillary thyroid cancer, which constitutes up to 80 percent of all thyroid cancer cases, develops from glandular epithelial cells that normally produce the essential iodine-containing thyroid hormones (448). Approximately 10-20 percent of people with papillary thyroid cancer have RET fusion-positive tumors, and roughly 90 percent of patients with advanced medullary thyroid cancer, a less common form of thyroid cancer, carry RET mutations (449). Traditionally, patients with RET-altered thyroid cancers are treated with nonselective therapies, with only a modest efficacy and significant side effects. Promising results from the same basket trial that showed the efficacy of pralsetinib for patients with NSCLC harboring RET alterations prompted FDA to expand the use of pralsetinib for treatment of patients with thyroid cancer. In December 2020, pralsetinib was approved for treatment of adult and pediatric patients 12 years of age and older with advanced or metastatic medullary thyroid cancer (MTC) harboring alterations in the RET protein who require systemic therapy or patients with RET fusion-positive thyroid cancer who require systemic therapy, and who have developed resistance to treatment with radioactive iodine. Pralsetinib demonstrated durable clinical activity, as measured by tumor shrinkage among other parameters, in thyroid cancer patients with or without prior therapy, regardless of what type of RET genetic alteration was present in tumors. Almost 80 percent of patients who responded to the treatment experienced a response lasting for six months or more (450).

In May 2021, FDA granted accelerated approval to infigratinib (Truseltiq) for adults with locally advanced or metastatic bile duct cancer, harboring alterations (fusion or other

rearrangement) in the tyrosine kinase protein fibroblast growth factor receptor 2 (FGFR2), that had been previously treated and could not be removed surgically. The FDA also approved a companion diagnostic test for selection of patients with FGFR2 fusion or other rearrangement for treatment with infigratinib. While rare—roughly 8,000 cases diagnosed in the United States annually—the 5-year relative survival rate for metastatic bile duct cancer (also known as cholangiocarcinoma) is only two percent (3). More than seven percent of patients with bile duct cancer harbor alterations in FGFR proteins (451). Infigratinib selectively binds to and inhibits the activities of FGFR1, 2, and 3, and induces cancer cell death by blocking tumor cell proliferation (452). Efficacy of infigratinib was determined in a phase II clinical trial. Infigratinib was given to 108 bile duct cancer patients. Among the 23 patients whose tumors shrank substantially with the treatment, 8 patients maintained the response for 6 months or more (453). Infigratinib is only the second FGFR-specific inhibitor approved by FDA, after erdafitinib (Balversa) that was approved in April 2019 to treat certain patients with bladder cancer, and covered in the *AACR Cancer Progress Report 2019* (454). Additional clinical studies will be necessary to determine whether infigratinib can also treat the more than seven percent of patients with cancer types, such as cervical, colon, endometrial, and esophageal cancers, whose tumors also harbor alterations in FGFR (455).

Inhibiting the Blood Supply to Tumors

Angiogenesis is the formation of a network of blood vessels that supplies nutrients to newly formed tissues during normal development. In 1970, researchers first posited that tumors secrete factor(s) to drive blood vessel formation in and around the tumor, thus establishing a "supply chain" of nutrients for tumors to grow and spread (456). Fifty years of discovery science since then have led to the identification of key molecules that are necessary for tumor angiogenesis. Researchers have leveraged this knowledge to develop molecules, sometimes called antiangiogenic drugs or angiogenesis inhibitors, that inhibit tumor angiogenesis (**Figure 21**, p. 98) (457). Clinical breakthroughs stemming from this research are highlighted by the development and FDA approval of 12 angiogenic inhibitors—including tivozanib (Fotivda) approved in March 2021—to treat a wide range of solid tumors.

Renal cell carcinoma (RCC) is the most common type of kidney cancer. An estimated 76,080 new cases of kidney cancer will be diagnosed in the United States in 2021, and nine out of 10 will be RCC cases (3). Despite the availability of an array of treatment options, patients with advanced RCC, which develops in the lining of small tubes in kidneys, have a poor 5-year survival rate of only 13 percent (3). In March 2021, FDA approved tivozanib for adult patients with RCC whose disease had relapsed or became nonresponsive following two or more systemic therapies. Tivozanib is a potent inhibitor of vascular endothelial growth factor receptors (VEGFR), which play an essential role in tumor angiogenesis (457). The phase III clinical trial evaluating efficacy of tivozanib compared the responsiveness of RCC patients treated with tivozanib with those treated with sorafenib (Nexavar), another molecularly targeted therapeutic that inhibits angiogenic as well as other cancer-causing proteins and has been approved by FDA to treat RCC (458). Tivozanib treatment increased disease-free survival by nearly two months (5.6 months) when compared to sorafenib (3.9 months). The objective response rate—a measure of how well a patient responds to a treatment as determined by the reduction in size of the tumor after the treatment, among other parameters—more than doubled for RCC patients treated with tivozanib (459).

Delivering Cytotoxic Agents Precisely to 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 of precision anticancer therapeutics (see **Figure 22**, p. 102). The antibody used in an ADC is directed against a protein that is overexpressed 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 how stable the toxin is inside the body. Once 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 (460). This approach minimizes the side effects of the cytotoxic agent compared to a traditional systemic delivery.

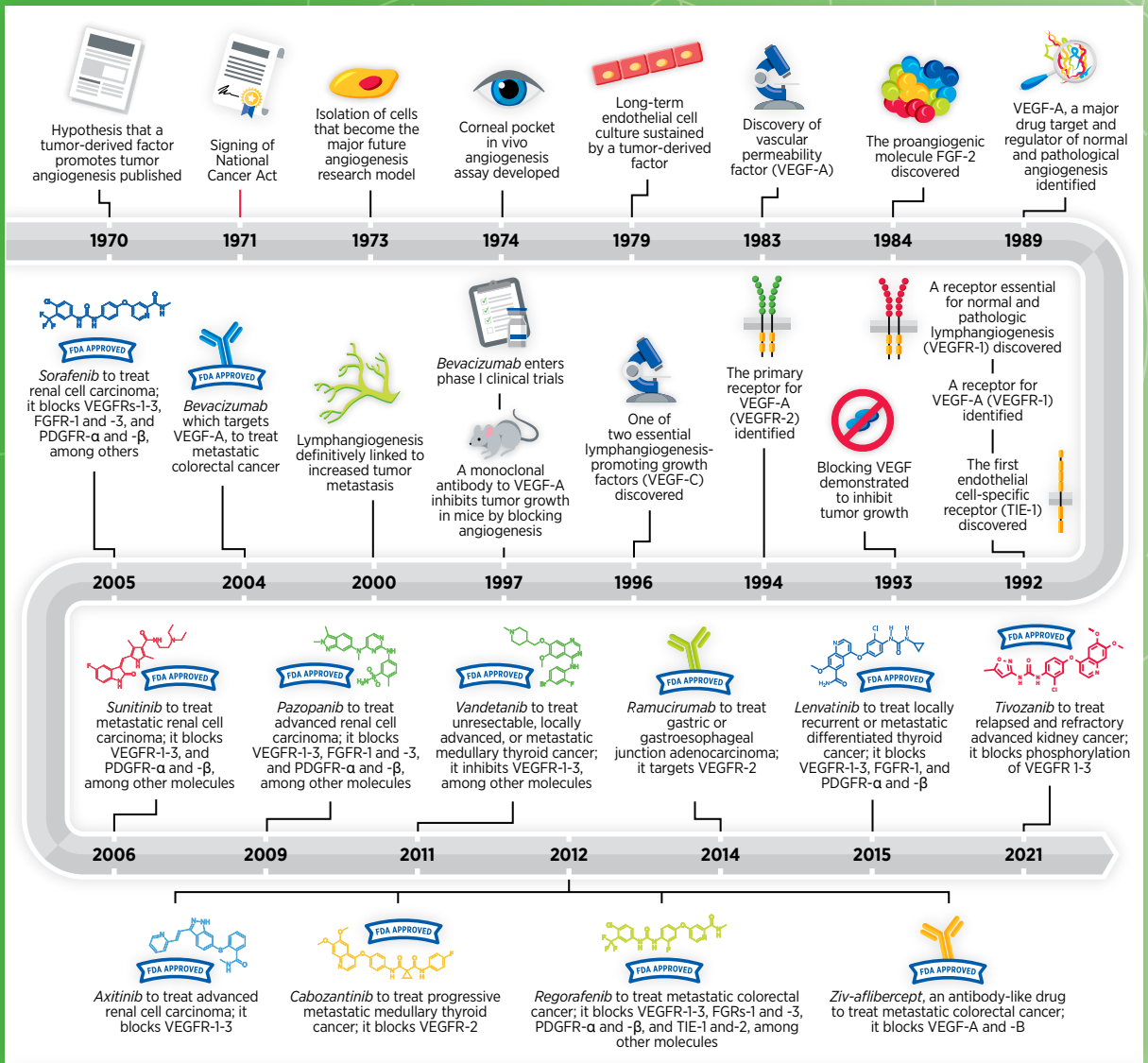
The past two decades have seen remarkable progress against multiple myeloma, with 20 therapies available today and a declining mortality rate from the cancer (see sidebar on **Two Decades of Progress Against Multiple Myeloma**, p. 91). Most patients with multiple myeloma respond well to the initial treatment regimen. Unfortunately, the disease often relapses and patients become resistant to currently available therapies (461). Up until 2021, the antibody-based molecularly targeted therapeutics approved by FDA to treat multiple myeloma were directed against one of two proteins, CD38 [daratumumab (Darzalex) and isatuximab-irfc (Sarclisa)] or SLAMF7 [elotuzumab (Empliciti)], that are found on the surfaces of normal plasma cells and are overexpressed in multiple myeloma cells.

Approval of belantamab mafodotin-blmf (Blenrep) marks a significant therapeutic milestone—and is designated a first-in-class drug by FDA because it is directed against a different cell surface protein, B-cell maturation antigen (BCMA), which is present in abundance on multiple myeloma cells (462). Using BCMA to deliver a cytotoxic agent to multiple myeloma cells raises hope for patients who have developed resistance to anti-CD38-antibody-based treatments. In belantamab mafodotin-blmf, the anti-BCMA antibody is conjugated with an inhibitor of microtubules, which are a component of the cellular cytoskeleton and have a number of functions including cell division. Thus, inhibition of microtubules prevents cells from multiplying and ultimately results in cell death. The clinical trial investigating the efficacy of belantamab mafodotin-blmf only included multiple myeloma patients who had received three or more prior treatments and had stopped

FIGURE 21

NATIONAL CANCER ACT
50 YEARS
1971-2021

TARGETING TUMOR'S BLOOD SUPPLY TO CURE CANCER: MILESTONES FROM THE PAST 50 YEARS



Since the hypothesis 50 years ago that tumors secrete a factor that enhances formation of new blood vessels (angiogenesis) in and around the tumor tissue, breakthrough discoveries have fueled the development of molecularly targeted therapeutics that inhibit tumor angiogenesis and result in tumor shrinkage and/or elimination. Since 2005, the U.S. Food and Drug Administration (FDA) has approved 12 such anticancer therapeutics, also called antiangiogenic agents. Bevacizumab (Avastin) was the first of these drugs to be approved in 2004, and tivozanib (Fotivda) was the most recent, in 2021. Research into angiogenesis under both normal and pathological conditions, including cancer, helped identify many of the molecular regulators of these processes, and these regulators are the specific targets of the 12 antiangiogenic agents. The year when each of these therapeutics was first approved is indicated on the timeline; however, most of these agents received approval from FDA for the treatment of additional cancers in subsequent years (see **Angiogenesis Inhibitors** in **Supplemental Table 2**, p. 185).

responding to a proteasome inhibitor, an immunomodulatory agent, and an anti-CD38 antibody therapy. Nearly one third of all treated patients responded to belantamab mafodotin-blmf, and 73 percent of patients who responded showed a response duration of six months or more (463). Importantly, the use of BCMA to direct cytotoxic agents or engineered T cells to cancer cells (see **Engineering Immune Cells to Fight Cancer**, p. 115) provides new options for targeting multiple myeloma with anticancer therapeutics.

Another ADC approved by FDA during the 12 months covered in this report is loncastuximab tesirine-lpyl (Zynlonta). Loncastuximab tesirine-lpyl comprises an antibody directed against CD19—a protein found in abundance on the surface of cancerous B cells (464)—conjugated with a chemotherapeutic alkylating agent that irreversibly binds to DNA and blocks cell division. The FDA approved loncastuximab tesirine-lpyl for adult patients with relapsed or refractory large B-cell lymphoma—including diffuse large B-cell lymphoma (DLBCL)—who have received two or more lines of systemic therapy. DLBCL is the most common type of non-Hodgkin lymphoma (NHL) in the United States, accounting for about one out of every three lymphomas (3). DLBCL is an aggressive NHL that affects a type of white blood cells called B-lymphocytes, and despite recent treatment advances, such as the use of anti-CD20 monoclonal antibody rituximab (Rituxan), approximately 40 percent of patients relapse or show poor response (465). Efficacy of loncastuximab tesirine-lpyl was evaluated in 145 adult patients who participated in a phase II clinical trial. Nearly 50 percent of patients responded favorably to treatment with loncastuximab tesirine-lpyl and showed a significant decrease in cancer. Importantly, DLBCL was undetectable in nearly 25 percent of responders for at least 10 months (466).

In January 2021, FDA expanded the use of the ADC fam-trastuzumab deruxtecan-nxki (Enhertu), originally approved in December 2019 for the treatment of metastatic HER2-positive breast cancer (467), to treat HER2-positive gastric (stomach) or gastroesophageal junction (GEJ) adenocarcinomas, after they had progressed on trastuzumab therapy. Gastric cancer accounts for about 1.5 percent of all cancer cases in the United States, with an estimated 26,560 new diagnoses in 2021 (3). Currently there are no tests for the early detection of gastric cancers among average-risk individuals. As a result, gastric cancer is often diagnosed at an advanced stage when it is difficult to treat and has a very poor 5-year relative survival rate of less than 20 percent (3). Roughly 22 percent of gastric cancer patients have tumors with abnormally high levels of the protein HER2, and HER2-overexpression remains an important biomarker for the selection of patients eligible for anti-HER2 targeted therapies (468) (see sidebar on **Biomarkers and Their Use in Cancer Science and Medicine**, p. 103). However, in contrast to HER2-positive breast cancer, HER2-targeted treatments in the past did not improve outcomes for patients with gastric cancer whose disease had progressed on trastuzumab treatment (469). Treatment of patients with HER2-positive gastric cancer with fam-trastuzumab deruxtecan-nxki increased overall survival by four months compared to patients treated with standard chemotherapy. Furthermore, the objective response rate (see **Table 6**, p. 87) was reported in 51 percent of the patients in the trastuzumab deruxtecan group, as compared to 14 percent of those who received chemotherapy(470). Therefore, approval of fam-trastuzumab deruxtecan-nxki is an important advance toward expanding targeted therapy options for gastric cancer patients like **Bryan Chagolla** (see p. 100).

In the 12 months covered in this report FDA also expanded the use of sacituzumab govitecan-hziy (Trodelvy)—an ADC previously approved to treat locally advanced or metastatic triple-negative breast cancer—for the treatment of locally advanced or metastatic urothelial cancer patients who have been previously treated with standard chemotherapy and at least one checkpoint inhibitor. Seventy-seven percent of patients with locally advanced or metastatic urothelial cancer who responded to the sacituzumab govitecan-hziy treatment showed a decrease in detectable cancer; progression-free survival (see **Table 6**, p. 87) was 5.4 months and the median overall survival was nearly 11 months following the treatment (472). An estimated 83,730 Americans—64,280 men and 19,450 women—will be diagnosed with bladder cancer in 2021, and 90 percent of those cases will be urothelial cancer. The relative 5-year survival rate for patients with metastatic urothelial cancer is only 5.5 percent (3). Thus, the expansion of sacituzumab govitecan-hziy use to treat metastatic urothelial cancer provides a valuable additional treatment option for these patients.

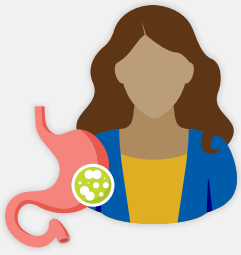
Collectively, the approval of two new ADCs and expansion of two previously approved ADCs between August 1, 2020 and July 31, 2021 highlights the accelerated innovations in the development of these unique and powerful targeted therapeutics that can transform the lives of many patients with cancer.

Expanding Treatment Options for Patients with Rare Blood Cancers

Blood or hematologic cancers arise in the bone marrow where blood is formed, or in cells of the immune system. In the 12 months covered in the report, FDA has made numerous decisions that are transforming the lives of patients with a wide array of blood cancer types (see sidebar on **Recent Advances against Blood Cancers**, p. 105). Some of these approvals are expanding treatment options for patients with very rare forms of blood cancers.

Continued on page 102 ▸

In the United States, the incidence of **stomach cancer was nearly twice as high among Hispanics** as it was among non-Hispanic whites in 2018, the most recent year for which such data are available (3).



BRYAN CHAGOLLA AGE 40 | Monterey Park, California

Maintaining Balance in Life, Despite Metastatic Gastric Cancer

I was sitting in a tiny room of my local emergency room waiting for my test results when the doctor came in, grabbed my hand, and said, "We're 95 percent sure it's cancer." I had an immediate feeling of despair, denial, and shock. It felt like darkness, like I was sinking into a void. One week later, I received my official diagnosis of stage IV gastric cancer. After a series of initial treatments, I was put on a newly approved drug called fam-trastuzumab deruxtecan-nxki (Enhertu). Since then, my cancer markers have gone down drastically, and the scans show continued shrinkage of the tumor. I am maintaining life balance and calm, focusing on the present, and spending time with family.

It all started in January of 2019. I was experiencing some abdominal symptoms such as loss of appetite, indigestion, heartburn, and difficulty eating. Between January and April, I lost nearly 40 pounds. I also had abdominal pain and started feeling faint throughout the day. Because of some issues with my health insurance, I did not have coverage during this time but decided to see a physician as my symptoms were getting worse. My doctor recommended some dietary changes and ordered a few standard laboratory tests. None of the test results were abnormal, but my symptoms got progressively worse. At the time my wife and I were expecting our second child and I thought that I would wait until she was born to take care of myself. One day that June, however, the pain became so severe that I had no choice but to go to the emergency room.

They performed an ultrasound and a CT exam after which I was told they were 95 percent sure it was cancer. I was 38 years old with a young daughter and another child on the way. I was in complete shock. They needed to do a biopsy to be certain. I was sent home with pain medications as I was waiting for my biopsy results. A week later I was in so much pain that my sister had to drive me to the hospital. At a friend's suggestion, I went to Cedars Sinai where I received my official diagnosis of stage IV gastric (stomach) cancer. My sister works as a medical administrator and has been a guardian angel for me. She helped me navigate the health care system and get back on health insurance. She also helped me find an oncologist at the City of Hope Comprehensive Cancer Center, which is where I received all my treatments.

Genetic testing of the cancer revealed that it was HER2 positive. My initial treatment was a chemotherapy regimen known as FOLFOX combined with a HER2-targeted agent called Herceptin. It was a biweekly treatment that I received for about six months. The treatment was quite effective. It reduced my tumors. I had a large tumor on my esophageal juncture that had spread to the liver and over the course of treatment that tumor shrank by 75 percent. However, I was also starting to experience some serious side effects. I had severe neuropathy in my hands and feet, and difficulty eating and putting on weight. Because my tumor was responding so well, my oncologist decided to remove one of the chemotherapeutic agents in FOLFOX and put me on a modified chemotherapy regimen along with Herceptin. I received this treatment from January 2020 until about November. In addition to my chemo, I was also trying some alternative medicine approaches, including nutritional guidance and acupuncture. Overall, I was doing well. I had gained some weight and my tumor seemed stable.

In June of 2020, while I was still on the modified chemotherapy, my lab tests showed that the level of one of the cancer markers, carcinoembryonic antigen (CEA), was increasing. Since my tumors were still shrinking according to the scans from earlier that year, we decided to wait and watch. By October, the levels of CEA had skyrocketed, and my scans also confirmed that the tumors were growing again. My oncologist suggested a clinical trial that was testing a combination of two molecularly targeted therapies. I started on the trial in early January. Unfortunately, I experienced some serious adverse effects and had to discontinue the treatments. Luckily, in mid-January 2021, the FDA approved the HER2-targeted therapeutic called fam-trastuzumab deruxtecan-nxki for patients with gastric cancer. In early February I started receiving the new treatment and have been on this drug ever since. I do get some fatigue and nausea after treatment, but these side effects are less severe and more manageable compared with FOLFOX.

Since I've been on fam-trastuzumab deruxtecan-nxki, my CEA levels have declined drastically. A scan in May 2021 confirmed that my tumors are shrinking again.

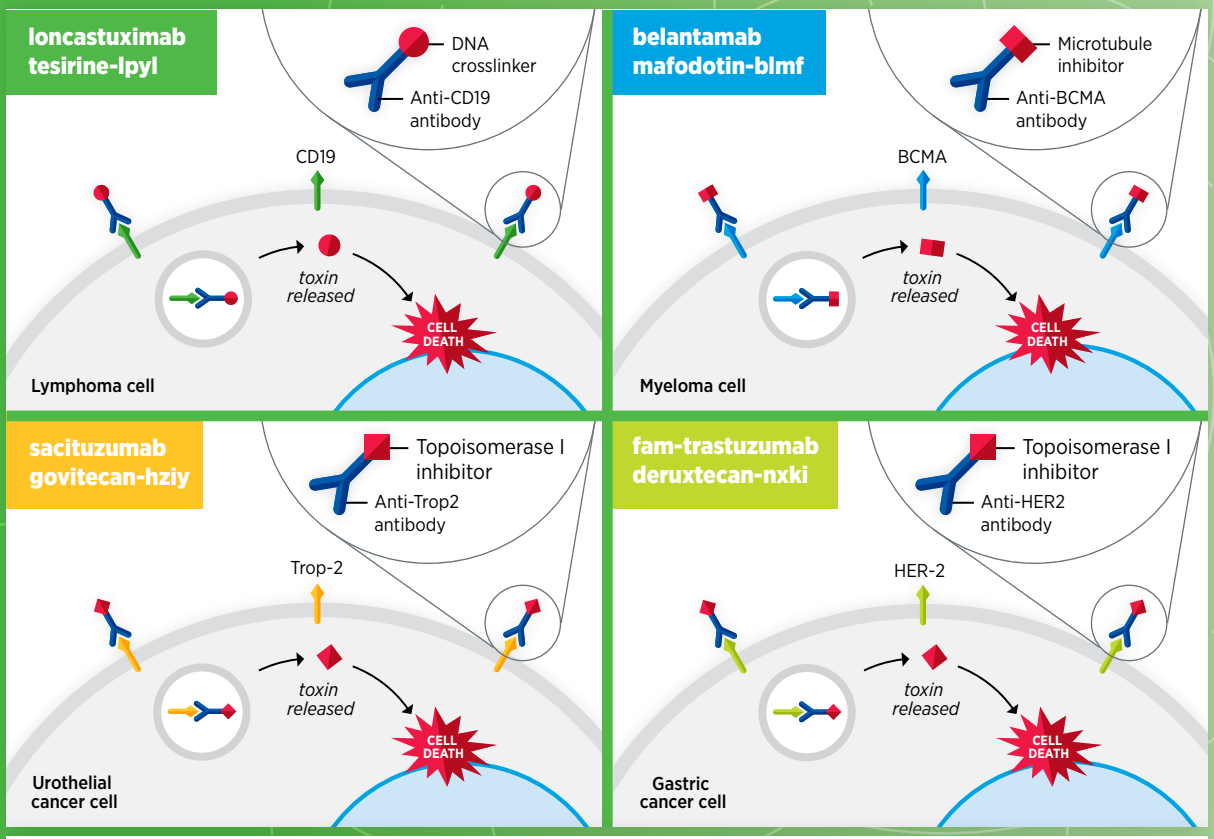
I am grateful that the treatment is working. I am also thankful to have a very supportive family and home life. I feel that I am at a place that is stable and consistent, and my goal is to keep things this way and continue to work toward improving. What my experience has taught me is that I must maintain my balance and calm. Right now, I am focusing on my mental, physical, and spiritual health and spending time with my family and loved ones.

In September 2021, tests found that the tumor at the top of Bryan's liver was growing again and a biopsy found that the cancer was no longer HER2 positive. Bryan and his care team were developing a new treatment plan.

I am focusing on my mental, physical, and spiritual health and spending time with my family and loved ones.

FIGURE 22

DELIVERING CYTOTOXIC AGENTS PRECISELY TO CANCER CELLS



Between August 1, 2020 and July 31, 2021, FDA approved two new antibody-drug conjugates (ADCs), belantamab mafodotin-blmf (Blenrep) and loncastuximab tesirine-lpyl (Zynlonta), to treat multiple myeloma and large B-cell lymphoma, respectively. The approval of another ADC, fam-trastuzumab deruxtecan-nxki (Enhertu)—first approved by FDA in 2019 to treat HER2-positive metastatic breast cancer—was expanded to treat HER2-positive gastric or gastroesophageal junction (GEJ) cancers, increasing the targeted therapy options for gastric cancer patients like **Bryan Chagolla** (see p. 100). The FDA also expanded the use of sacituzumab govitecan-hziy (Trodelvy), an ADC previously approved to treat locally advanced or metastatic triple-negative breast cancer for the treatment of certain patients with bladder cancer.

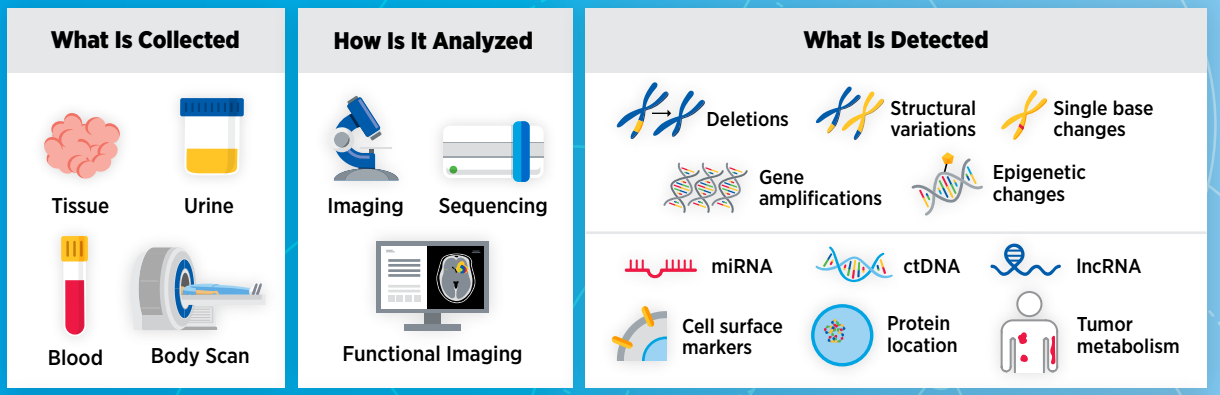
The antibody portion of belantamab mafodotin-blmf recognizes the B-cell maturation antigen (BCMA), a protein that is present in abundance on the surface of multiple myeloma cells. The antibody is attached to a cytotoxic agent that blocks microtubules, the structural proteins that are necessary for cell multiplication. Once internalized, the cytotoxic drug is released inside the cell, where it inhibits microtubules and blocks cell division.

In case of loncastuximab tesirine-lpyl, the antibody is directed against CD19, a protein located on the surface of normal B cells and lymphoma cells, and is attached to a cytotoxic agent that irreversibly binds to DNA and prevents cells from dividing.

Fam-trastuzumab deruxtecan-nxki binds to the HER2 protein present on the surface of tumor cells for certain types of breast and gastric cancer and delivers a cytotoxic agent that kills cancer cells by blocking a protein necessary for DNA duplication, an essential process for cell multiplication.

Sacituzumab govitecan-hziy carries an inhibitor against the same protein targeted by fam-trastuzumab deruxtecan-nxki, but the antibody portion of the ADC attaches to a different protein, called Trop-2, which is commonly found on the surface of breast and urothelial cancer cells.

BIOMARKERS AND THEIR USE IN CANCER SCIENCE AND MEDICINE



Use of Biomarkers in Cancer Research and Care: Selected Examples

BIOMARKER TYPE	CANCER TYPE	WHAT IS TESTED/HOW	CLINICAL PURPOSE
Risk Assessment	Breast cancer	A 70-gene panel (MammaPrint)/ DNA sequencing	To evaluate risk of recurrence
Diagnostic	Prostate cancer	PSMA (Ga 68 PSMA-11)/ Radiography	To diagnose metastatic prostate cancer
Monitoring	Leukemia	Immunoglobulin rearrangements (clonoSEQ)/DNA sequencing	To monitor minimal residual disease in leukemia
Prognostic	Breast and Prostate cancers	A 17-gene signature (OncotypeDX)/DNA sequencing	To assess the aggressiveness of cancer and to help manage treatment
Predictive	Multiple cancer types	MSI-H/dMMR/ DNA sequencing	To guide treatment and identify those at high risk of cancer recurrence after initial treatment
Response	Multiple cancer types	Nucleic acid sequences from patient's tumor (e.g., cfDNA) or proteins produced by tumors (e.g., CEA)	To assess treatment response and guide next course of action
Safety	AML	IDH1/2 mutations/ DNA sequencing	To determine what therapy will be safe for patients

According to the FDA, a biomarker is a defined characteristic that is measured as an indicator of normal and/or abnormal biological processes, or to determine responses to a therapeutic intervention. Molecular, histological, and physiological characteristics are all considered different types of biomarkers. Changes in structure, function, and/or location of all major types of molecules—DNA, RNA, and proteins—can be monitored using biomarkers.

Developed from (471).

Biomarkers are measurable in biological materials such as tissues, cells, and/or bodily fluids using a variety of techniques depending on the nature of the biomarker. The FDA uses the **B**iomarkers, **E**ndpoint**S** and other **T**ools (BEST) glossary to characterize biomarkers into seven categories that include risk assessment, diagnosis, monitoring, prognosis, prediction, responsiveness, and safety.

Lymphoma is a type of blood cancer that develops when B- or T-cell lymphocytes, the white blood cells that are primarily involved in the body's adaptive immune system, or less commonly natural killer (NK) cells that are involved in both the innate and adaptive immune response, grow out of control. There are more than 70 different types of lymphoma, ranging from slow growing

to highly aggressive forms. The most common type of lymphoma, called non-Hodgkin lymphoma (NHL), accounts for four percent of all cancers in the United States (3). About 85 percent of all NHL originate from B-cell lymphocytes (473). Recent advances in treatment of NHL have markedly improved survival rates and quality of life for patients (3). Although some forms of B-cell NHL, such as follicular lymphoma (FL) and marginal zone lymphoma (MZL), respond well to initial treatments, they remain difficult to cure because many patients develop resistance to the treatment (474). Additionally, these lymphomas are rare which can make it challenging for researchers to study and for clinicians to treat these diseases (see sidebar on **The Challenges Posed by Rare Cancers**, p. 106).

In February 2021, FDA granted accelerated approval to umbralisib (Ukoniq) for treatment of patients who have relapsed or refractory MZL and have received at least one prior anti-CD20-based therapy. Umbralisib, a selective inhibitor of an enzyme—PI3K delta—which is primarily expressed in tumor cells and helps them grow (475)—was also approved to treat patients with relapsed or refractory FL who have received at least three prior treatments. The decision was based on a randomized phase II trial in which nearly half of the MZL patients treated with umbralisib showed a significant decrease in cancer burden, and about 16 percent of the patients were free of any signs of cancer (476,477). For patients with FL, the overall response rate to the treatment was 43 percent and three percent of the patients showed no signs of disease at the end of the treatment. The approval of umbralisib has given hope to patients with otherwise incurable blood cancers.

Another key therapeutic advance in treating a rare form of lymphoma is the expanded use of crizotinib (Xalkori)—originally approved in 2011 to treat certain patients with NSCLC that express an abnormal form of the ALK protein—for treatment of children and young adults who have relapsed or refractory anaplastic large cell lymphoma (ALCL) expressing aberrant forms of the ALK gene. Unlike MZL and FL which are derived from B-cell lymphocytes, ALCL originates from T-cell lymphocytes, and accounts for about two percent of lymphomas. ALCL tends to be fast-growing and accounts for 10 to 20 percent of lymphomas in children and young adults (3). The approval of crizotinib, which is a molecularly targeted therapeutic against ALK and MET proteins, to treat ALK-positive ALCL was based on findings from a phase II clinical trial. Eighty-one percent of patients who participated in the trial no longer showed any signs of the cancer. Of the patients who responded to the treatment, 39 percent maintained such a response for at least six months and 22 percent maintained response for at least a year following treatment (478). Treatment with crizotinib has transformed the lives of patients such as **Zachary (Zach) Witt**, who was highlighted in the *AACR Cancer Progress Reports* in 2014 and 2015 as a participant in the clinical trial evaluating the efficacy of crizotinib for treatment of ALK-positive ALCL patients (129,139).

In June 2021, FDA approved the molecularly targeted therapeutic avapritinib (Ayvakit) for treating adults with certain aggressive forms of a rare disorder known as advanced systemic mastocytosis. In patients with this disorder, immune cells called mast cells accumulate in internal organs such as the liver, spleen, bone marrow, and small intestine.

Research has shown that most cases of systemic mastocytosis are caused by mutations in the gene that encodes the KIT tyrosine kinase receptor, which is one of the targets of

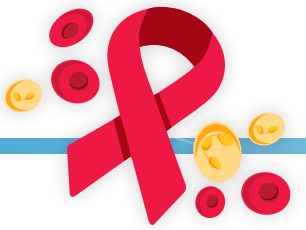
ZACHARY (ZACH) WITT
Age 16 | Pennsylvania

In 2010-2011, Zach was diagnosed with anaplastic large cell lymphoma with a particular genetic alteration—an ALK translocation—that made him eligible for a clinical trial of the ALK-targeted therapeutic crizotinib (Xalkori). As of April 2021, Zach has been on crizotinib for ten years and continues to do well. He turned 16 this summer and is finishing 10th grade. In his free time, Zach loves baseball, running, and working out. He also enjoys reading, playing piano, and being involved in his church youth group.

Top photo: ©2014 American Association for Cancer Research/Sherry Vitale. Bottom photo: Courtesy of Pam Witt.

RECENT ADVANCES AGAINST BLOOD CANCERS

In the 12 months from August 1, 2020 to July 31, 2021, the U.S. Food and Drug Administration made numerous decisions that are transforming the lives of patients with a wide array of hematologic cancers, including the following:



Acute Lymphoblastic Leukemia (ALL) and Lymphoblastic Lymphoma (LBL)

- Asparaginase erwinia chrysanthemi (recombinant)-rywn (Rylaze) is a component of a multi-agent chemotherapeutic regimen, for the treatment of those who have developed hypersensitivity to E. coli-derived asparaginase, that was approved in June 2021.

Acute Myeloid Leukemia

- Azacitidine (Onureg) is an epigenome-modifying agent approved in September 2020.

Anaplastic Large Cell Lymphoma

- Crizotinib (Xalkori) is a molecularly targeted therapeutic approved in January 2021.

Large B-cell Lymphoma

- Lisocabtagene maraleucel (Breyanzi) is an immunotherapeutic approved in February 2021.
- Loncastuximab tesirine-lpyl (Zynlonta) is a molecularly targeted therapeutic approved in April 2021.

Follicular Lymphoma

- Umbralisib (Ukoniq) is a molecularly targeted therapeutic approved in February 2021.
- Axicabtagene ciloleucel (Yescarta) is an immunotherapeutic approved in March 2021.

Marginal Zone Lymphoma

- Umbralisib (Ukoniq) is a molecularly targeted therapeutic approved in February 2021.

Mast Cell Leukemia

- Avapritinib (Ayvakit) is a molecularly targeted therapeutic approved in June 2021.

Multiple Myeloma

- Belantamab mafodotin-blmf (Blenrep) is a molecularly targeted therapeutic approved in August 2020.
- Melphalan flufenamide (Pepaxto) is a chemotherapeutic approved in February 2021.
- Idecabtagene vicleucel (Abecma) is an immunotherapeutic approved in March 2021.

avapritinib. The approval of avapritinib for treating advanced systemic mastocytosis, including in patients with an associated hematological neoplasm and mast cell leukemia, was based on two clinical trial results. The data from the clinical trials showed that in 28 percent of patients all signs and symptoms of cancer disappeared, and, in another 28 percent, there was a reduction in the extent of cancer in the body following treatment with the molecularly targeted therapeutic.

Inhibiting the Progression of Prostate Tumors and Improving Quality of Life

In patients with advanced prostate cancer, the tumors use testosterone and other androgens, hormones naturally produced by the body, to stimulate cell division and metastasis. These patients are typically treated with androgen deprivation therapy (ADT). One class of drugs used in ADT is agonists of gonadotrophin-releasing hormone (GnRH), a hormone that acts on pituitary gland and decreases the production of testosterone. A commonly used GnRH agonist is leuprolide (Lupron), which is given via injection every few months. Leuprolide reduces the production of testosterone, thus starving advanced prostate cancer of the fuel that it needs to grow and spread. A serious side effect of leuprolide (and other ADT drugs) is increased risk of heart attacks and heart failure, highlighting the need of new drugs without harmful effects for prostate cancer patients (479).

In December 2020, relugolix (Orgovyx)—a new drug to treat men with advanced prostate cancer—was approved by FDA. Relugolix is a GnRH antagonist, which also acts on the pituitary gland, but blocks testosterone production more directly and rapidly (480). In a large clinical trial, relugolix was more effective at reducing testosterone levels in men with advanced prostate cancer than leuprolide. About 97 percent of men treated with relugolix reached and maintained very low testosterone levels, compared to 89 percent of men who received leuprolide. Unlike patients treated with many other drugs used for ADT, men treated with relugolix also had significantly less serious cardiac issues, and restoration of their testosterone back to normal levels within a few months of stopping therapy (481). Another benefit of relugolix is that it is a tablet that patients can take every day, further minimizing any inconvenience to patients from intramuscular administration. Relugolix is a significant therapeutic advance that is expected

THE CHALLENGES POSED BY RARE CANCERS

The National Cancer Institute (NCI) considers a type of cancer rare if it occurs in fewer than 15 out of 100,000 people each year. All childhood cancers are considered rare cancers. Rare cancers pose significant challenges to many stakeholders in the cancer community, including patients, physicians, and researchers. These include:

Challenges for Patients

- The long time it takes from when they first notice a symptom to the time when doctors know that the symptom is caused by a rare cancer and what type of cancer it is.
- Finding a physician who is knowledgeable about the rare cancer with which they have been diagnosed and how to treat it.
- Often the necessity to travel far from location of primary residence to get treatment for a rare cancer.

Challenges for Physicians

- Lack of adequate training to treat a rare cancer with which their patient has been diagnosed.
- Lack of knowledge to discuss in-depth with the patient the treatment and management options for the rare cancer.
- Lack of subject matter experts who can answer questions about the rare cancer with which their patient has been diagnosed or identify someone to whom they can refer the patient.

Challenges for Researchers

- Not enough information about the rare cancer to develop hypotheses and address key questions.
- Not enough animal or cell models of the rare cancer to test their hypotheses.
- Not enough tumor samples from patients with the rare cancer for their research.
- Not enough patients with a given rare cancer to conduct a clinical trial testing a potential new treatment.

In recent years, many initiatives have been launched with the goal of accelerating the pace of basic, translational, and clinical research in rare cancers, including the following involving the National Institutes of Health (NIH) and NCI:

The 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, the goal of the IRCI is to conduct practice-changing clinical trials for patients with rare cancers. The founding members were subsequently joined by the French National Cancer Institute, the Canadian Clinical Trials Group, the Japan Clinical Oncology Group, and the Clinical Oncology Society of Australia. The initiative to date has convened working groups looking at 12 rare cancer types, opened seven trials, and completed trials in high-grade uterine sarcoma and metastatic anal cancer. Many other clinical trials are underway or planned.

The NCI Rare Tumor Initiative

Launched in 2013, the goal of the NCI Rare Tumor Initiative is to foster closer collaborations between basic and clinical scientists, patient advocacy groups, and industry partners in the field of rare tumors to facilitate the development of new approaches to treating patients with rare cancers.

Rare Tumor Patient Engagement Network

As part of the Cancer Moonshot, the NIH Center for Cancer Research is building the rare tumor engagement network to study selected rare pediatric and adult tumors and develop 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.

to substantially improve the quality of life for patients with advanced prostate cancer.

ADVANCES IN CANCER IMMUNOTHERAPY

Cancer immunotherapy unleashes the natural ability of a patient's immune system to fight cancer (482). More than a century of research indicated that our immune system could detect and destroy cancer cells. Insights gathered in recent decades into functioning of the immune system have also provided the necessary information to weaponize a patient's immune system against cancer (483). Knowledge gleaned from these discoveries has allowed for the development of therapeutics, known as immunotherapeutics, that harness the power of the immune system against cancer in multiple ways (see sidebar on **How Immunotherapeutics Work**, p. 108).

The remarkable success of a variety of immunotherapeutics in the clinic has firmly established cancer immunotherapy as the fifth pillar of cancer treatment (see **Figure 19**, p. 80). This is, in part, because of the durable response to these revolutionary treatments in some patients with metastatic cancer. It is, however, important to note that not all patients who receive immunotherapy have experienced such an incredible response to the treatment (484). Furthermore, immunotherapeutics currently approved by FDA treat only a subset of cancer types. Researchers are continuously investigating new and improved strategies to fully realize the potential of immunotherapeutics for all cancers. Numerous ongoing clinical trials are evaluating new and improved immunotherapeutics and testing the use of those we already have against additional types of cancer, alone or in combination with other types of cancer treatments (485,486). One area of active research is the use of NK cells—a type of immune cells that rapidly kill abnormal cells by releasing cytotoxic chemicals—to develop a new class of immunotherapeutics (487–489). Several clinical studies have established that the NK cell-based immunotherapeutics are safe for use in humans (490–492), rapidly kill tumor cells (493,494) and, importantly, can be developed from stored or "off-the-shelf" NK cells (495–498). Current efforts are focused on improving the ability to expand NK cells and enhance their function (499), as well as genetically modifying NK cells to increase their effectiveness against tumor cells (500).

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, 2020 and July 31, 2021, the 12-month period covered in this report (see **Table 5**, p. 81).

Releasing the Brakes on the Immune System

Decades of discovery science have shown that immune cells, called T cells, are naturally capable of destroying cancer cells. We have also learned that some tumor cells have developed ways to escape destruction by T cells. One of the mechanisms by which tumor cells evade elimination by T cells is by expressing high levels of certain proteins that attach to and trigger "brakes" on T cells and stop them from attacking cancers. These brakes are proteins on the surface of T cells and are called immune checkpoint proteins. Researchers have identified many checkpoint proteins and their binding partners on tumor cells involved in the process of inhibiting T cell activation, three of which—CTLA-4, PD-1, and PD-L1—have proven to be effective targets for drug development (482) (see **Figure 23**, p. 109). This knowledge has spurred a new class of therapeutics—called immune checkpoint inhibitors—that can trigger T cells to destroy cancer cells by releasing these brakes (501).

A key advantage of checkpoint inhibitors is their broad utility against cancer, as highlighted by FDA approvals of checkpoint inhibitors to treat multiple types of cancer (see **Figure 24**, p. 114). During the 12-month period covered in this report—August 1, 2020 to July 31, 2021—one of the most significant advances toward realizing the promise of checkpoint inhibitors for treatment of cancer is the FDA approval of a new checkpoint inhibitor, dostarlimab-gxly (Jemperli), to treat metastatic endometrial cancer. During this period, FDA also expanded the use of four previously approved checkpoint inhibitors—cemiplimab-rwlc (Libtayo), nivolumab (Opdivo), pembrolizumab (Keytruda), and ipilimumab (Yervoy)—to treat additional types of cancer. As of July 31, 2021, one or more checkpoint inhibitors have been approved for treating 18 types of cancer and for treating any types of solid tumors that are characterized by certain molecular characteristics, such as microsatellite instability (MSI)–high, DNA mismatch–repair deficiency (dMMR), and tumor mutational burden (TMB)–high.

Endometrial cancer is the most common cancer of the female reproductive organs that develops in the inner lining of the uterus. An estimated 66,570 new cases of endometrial cancer (most common type of uterine cancer) will be diagnosed in 2021 (3). About 75 percent of endometrial cancers are diagnosed at an early stage and are curable with surgery. Women whose cancer continues to advance or returns after initial treatment with chemotherapeutics, however, have limited treatment options (502). Approximately 25-30 percent of patients with advanced endometrial cancer also have a specific genetic biomarker, called deficient mismatch repair (dMMR) (503), that can be determined by an FDA-approved test.

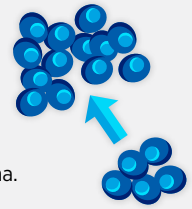
In April 2021, FDA granted accelerated approval to a new checkpoint inhibitor dostarlimab-gxly for treating patients with recurrent or advanced endometrial cancer that has progressed despite chemotherapy and whose cancers have the dMMR biomarker (see sidebar on **Biomarkers and Their Use in Cancer Science and Medicine**, p. 103). Dostarlimab-gxly is a monoclonal antibody that binds to the PD-1 protein—one of the brakes on T cells—and inhibits its activity, thus unleashing the immune system to kill cancer cells. The decision by FDA to approve dostarlimab-gxly was based on results from a basket clinical trial (see sidebar on **Types of Clinical Trials**, p. 75). Findings from the trial showed that the tumors either completely disappeared or shrank significantly in more than 40 percent of women who had dMMR recurrent or advanced endometrial cancer and were treated with dostarlimab-

HOW IMMUNOTHERAPEUTICS WORK

Immunotherapeutics utilize multiple ways 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, dostarlimab-gxly (Jemperli), the newest and the eighth member of this class of immunotherapeutics approved in April 2021 (see **Releasing the Brakes on the Immune System**, p. 107).

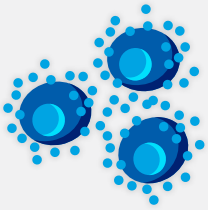
Some amplify the killing power of the immune system by providing more cancer-targeted immune cells called T cells, for example, the revolutionary idecabtagene vicleucel (Abecma) approved in March 2021 to treat relapsed or refractory multiple myeloma.



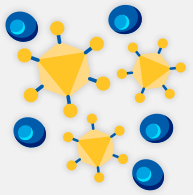
Some enhance the cancer-killing power of the immune system by triggering cancer-fighting T cells; these are called therapeutic cancer vaccines, for example, sipuleucel-T (Provenge).

Some flag cancer cells for destruction by the immune system, for example naxitamab-gqgk (Danyelza) that was approved by FDA in November 2020 to treat high-risk neuroblastoma.

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



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).



gxly. Importantly, the response lasted for six months or more in 93 percent of women who responded to the treatment (504). While many ongoing clinical studies are investigating the enormous potential of dostarlimab-gxly in treating additional cancer types, it has already transformed the lives of many patients with endometrial cancer, such as **Patricia Hawkins** (see p. 110).

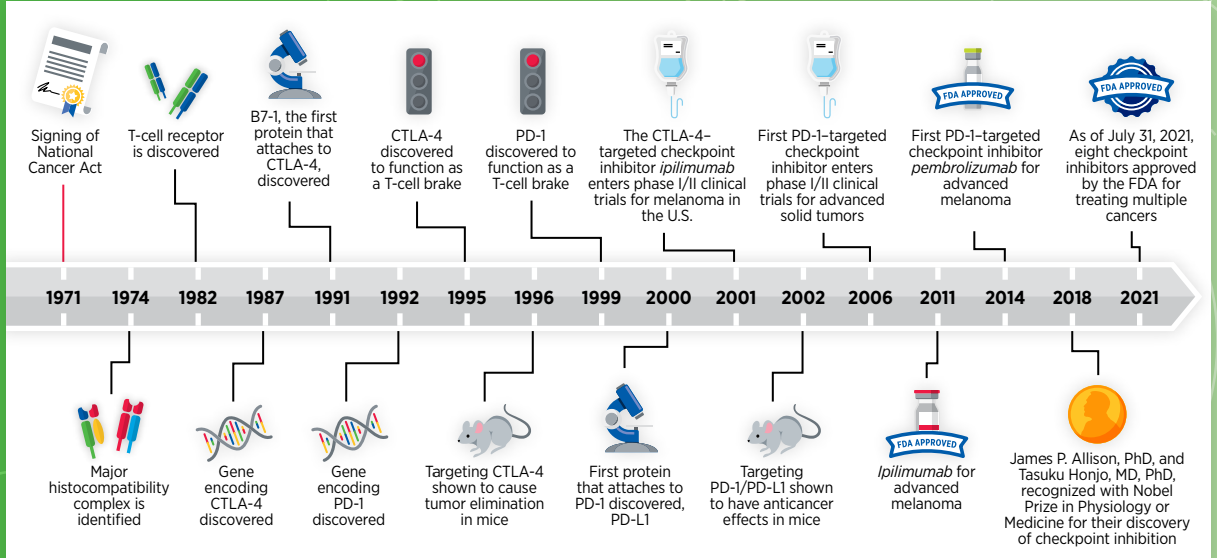
In October 2020, FDA granted approval to a combination of two checkpoint inhibitors—nivolumab and ipilimumab—as first-line treatment for adult patients with malignant pleural mesothelioma that cannot be removed by surgery. Mesothelioma—although rare, with about 3,000 cases diagnosed each year in the United States—is an aggressive cancer with 5-year relative survival rate of less than 20 percent (3). Mesothelioma originates in the thin layer of tissue that covers the majority of internal organs; pleural mesothelioma affects tissue that surrounds lungs (505). Patients with malignant pleural mesothelioma that cannot be surgically removed and those who did not receive any previous anticancer therapy were randomly assigned to receive a combination of nivolumab and ipilimumab or standard chemotherapy for up to 2 years. Overall survival was significantly extended among patients treated with the combination of nivolumab and ipilimumab (18.1 months) compared to those who received chemotherapy (14.1 months). The 2-year overall survival rate (see **Table 6**, p. 87) was 41 percent versus 27 percent for patients treated with a combination of the two checkpoint inhibitors versus those who received chemotherapy, respectively (506). This is remarkable progress toward treating a devastating type of cancer and brings the transformative power of immunotherapy to mesothelioma patients, such as **Susan Falbo** (see p. 112).

Skin cancer is one of the most common cancer types, with an estimated 5.4 million cases diagnosed each year in the United States. Two of the most common forms of skin cancer are called squamous cell carcinoma (SCC), which accounts for about 20 percent of the nonmelanoma skin cancer cases, and basal cell carcinoma (BCC), which makes up 80 percent of the nonmelanoma skin cancer diagnoses (3). Both forms originate from two different skin cell types—squamous and basal—that, together with a third type of cells called melanocytes, make up the top layer of skin. The FDA originally approved the immune checkpoint inhibitor cemiplimab-rwlc in September 2018 for treatment of advanced SCC. In February 2021, FDA expanded the use of cemiplimab-rwlc as the first immunotherapy for patients with locally advanced or metastatic BCC who were previously treated with a hedgehog pathway inhibitor (HHI), a type of molecularly targeted therapeutic, or for whom HHI was not appropriate. Approval was based on the findings that 79

FIGURE 23

NATIONAL CANCER ACT
50 YEARS
1971-2021

50 YEARS OF BREAKTHROUGHS IN DEVELOPING IMMUNE CHECKPOINT INHIBITORS



Checkpoint inhibitors are cancer immunotherapeutics that work by releasing "brakes" called immune checkpoint proteins on the surface of cancer-fighting immune cells called T cells. The first checkpoint inhibitor approved by the U.S. Food and Drug Administration (FDA) was ipilimumab (Yervoy) in March 2011. Ipilimumab targets an immune checkpoint protein on T cells called CTLA-4. Several other checkpoint inhibitors target a second immune checkpoint protein called PD-1. The first of these immunotherapeutics approved by FDA was pembrolizumab (Keytruda) in September 2014. More than 20 years of rapid advances in basic and clinical research underpinned the development of ipilimumab and pembrolizumab, starting with the discoveries of the CTLA-4 and PD-1 genes in 1987 and 1992, respectively. Other basic research milestones along the way to the FDA approvals include the identification of the brake function of CTLA-4 and PD-1, identification of the proteins that attach to and trigger the brake function of CTLA-4 and PD-1, and the demonstration that immunotherapeutics targeting these brakes can protect them from being triggered. Two researchers whose pioneering work established the paradigm of checkpoint inhibitors, James P. Allison, PhD, and Tasuku Honjo, MD, PhD, were recognized with the 2018 Nobel Prize in Physiology or Medicine for "their discovery of cancer therapy by inhibition of negative immune regulation." In April 2021, a new checkpoint inhibitor, dostarlimab-gxly, which targets the PD-1 protein, became the eighth FDA-approved checkpoint inhibitor available to treat cancer patients.

percent of locally advanced BCC and all metastatic BCC patients who responded to the treatment maintained their response for at least six months (507).

In February 2021, cemiplimab-rwlc was also approved as the first line of treatment for patients with advanced NSCLC whose tumors do not have any aberrations in EGFR, ALK or ROS1 proteins and have high expression of PD-L1, one of the proteins on cancer cells that apply the PD-1 brake on T-cells, as determined by an FDA-approved test. With this decision, cemiplimab-rwlc becomes the sixth checkpoint inhibitor approved by FDA for treatment of patients with NSCLC. The assessment was based on encouraging results from a randomized clinical trial comparing the outcomes of advanced NSCLC patients treated with either cemiplimab-rwlc or standard chemotherapy. More patients responded to cemiplimab-rwlc treatment compared to chemotherapy (37 percent versus 21 percent, respectively), and overall survival was increased by nearly eight months (22.1 months versus 14.3 months, respectively) (508).

Continued on page 114 ▸

PATRICIA HAWKINS AGE 52 | Farmville, Virginia

A Conversation with Patricia and Her Gynecologic Oncologist, Linda R. Duska, MD, MPH

PATRICIA

I was diagnosed with endometrial cancer in 2016. After my initial treatments with radiation and surgery the cancer came back. Fortunately, I was able to connect with Dr. Duska at the UVA Health in Charlottesville. Thanks to Dr. Duska and her team, I received treatment through a clinical trial that was testing dostarlimab-gxly (Jemperli) in patients with endometrial cancer. Since this treatment, I'm getting better, the tumor has shrunk, and I'm feeling good.

Back in 2016, my doctor prescribed tests due to some health issues, which eventually led to my diagnosis with endometrial cancer. It threw me for a loop. I was treated with surgery followed by radiation. After my initial treatment, I was doing well for about six months to a year when my left leg started to swell up. I figured that it was from the scar tissue that came from surgery but, as it turned out, my cancer had reappeared. This was upsetting. I received treatment with chemotherapy, but the cancer kept progressing. I kind of lost it there. I was crying a lot. My counselors helped me stay strong.

Eventually, I spoke with Dr. Duska and her team who talked to me about a clinical trial. At the beginning, I was a bit nervous but talking to Dr. Duska and her team gave me hope and I decided to participate.

The clinical trial was testing dostarlimab-gxly in patients with endometrial cancer. I received this drug for more than three years. The treatment has helped. I know I have made progress and that the cancer has shrunk. Sometimes, I get tired and I have some problems with my back. But I am glad that I participated in the trial and would tell other cancer patients to do so as well.

Now, I can spend time with my daughter and grandchildren. We have taken a few trips recently. I am also enjoying my time with my girlfriends. Sometimes I do get anxious about the cancer coming back. But I am ready to take on that challenge because I have a great doctor and I know that I will be taken care of well.

DR. DUSKA

Clinical research gives patients opportunities to try novel therapies. In the case of Patricia, the clinical trial gave her the opportunity to receive treatment with an immune checkpoint inhibitor, to which she would not have had access otherwise. Fortunately, she had a great response and was able to stay on the treatment for more than three years with a really good quality of life and an enjoyable time with her family. This was a great opportunity, and even though she was initially nervous about getting an experimental drug, Patricia was brave and did it. I'm very happy for her.

There are many reasons why it is important to improve the diversity of participants in clinical research. One of these reasons is to make sure that every patient has an opportunity to receive the novel therapeutics that are being tested in clinical trials. In addition, we want the results from these trials to be generalizable to a broader patient population, which means that, in the case of gynecologic cancers, we need them to be applicable to all women and not just a select few. Therefore, it is important that every woman with a gynecologic cancer who is eligible for a study is offered an opportunity to participate.

Clinical research is critical for making advances in cancer care, particularly in this new era of personalized medicine where, instead of a "one size fits all" approach, we're targeting therapy to the appropriate tumor in the appropriate patient. To do so effectively, we need a huge investment of time and money. The federal investment in cancer research allows us to have a less biased and more expert approach to clinical research. It is absolutely vital in helping us make progress in cancer care.

[But] I am glad that I participated in the trial and would tell other cancer patients to do so as well.

SUSAN FALBO AGE 63 | Shadyside, Ohio

Spending Quality Time with My Family Despite Mesothelioma, Thanks to Combination Immunotherapy

I was diagnosed with mesothelioma when I was 59. At the time, I was told that my only options were chemo- and radiation therapy and that I would be very lucky if I lived 12 to 18 months. I was not satisfied with that answer and my family and I did extensive research on the clinical trials that were evaluating new treatment options for patients with mesothelioma. Eventually, I was able to receive a combination of two immune checkpoint inhibitors, ipilimumab (Yervoy) and nivolumab (Opdivo). Since I have been on this treatment, my tumors have shrunk dramatically. I now have a great quality of life. I am able to play with my grandchildren and enjoy time with family.

My journey with cancer started about four years ago. My husband, two of our children, and I, all had what we thought were summer colds. After everyone else got over their colds, my illness persisted. I went to see a physician who initially treated me for pneumonia. However, I became hospitalized several times over that summer and wasn't getting any better. Finally, the doctors sent me for a lung biopsy, which led to my diagnosis of mesothelioma. After the diagnosis, the doctors recommended that I go home and get my affairs in order. I was told that radiotherapy and chemotherapy were my only treatment options and that, even with those, I would be lucky if I survived past 18 months. I was only 59 at the time and up until this diagnosis, I was very healthy. I had gone 20 years and never missed a day of work. So, to say this came as a complete shock would be a gross understatement.

Being the persistent and diligent person that I am, I started exploring the best course of action. My family and I researched everything that we could on mesothelioma. I was able to connect with a thoracic surgeon at the Mount Sinai Hospital in New York City, who had a lot of experience with patients with mesothelioma. My first treatment was a surgery known as lung decortication, followed by 30 rounds of radiation and chemotherapy. Although I did not do well with the chemotherapy, things seemed to be stable for about a year, but after that the tumors started to grow again. By this time, we had done more research on the newer therapies that were being evaluated for mesothelioma and I wanted to explore options other than chemotherapy. I heard about a clinical trial that was testing a combination of two immune checkpoint inhibitors, ipilimumab and nivolumab. To learn more, I traveled to the University of Chicago and met with the physician who was heading up the study. Even though I was a prime candidate for the trial—had all the cancer markers that were used to recruit participants—she informed me that it was too late to enroll. However, she conferred with my oncologist and, through some collaborations, I was still able to receive the treatment here in Ohio.

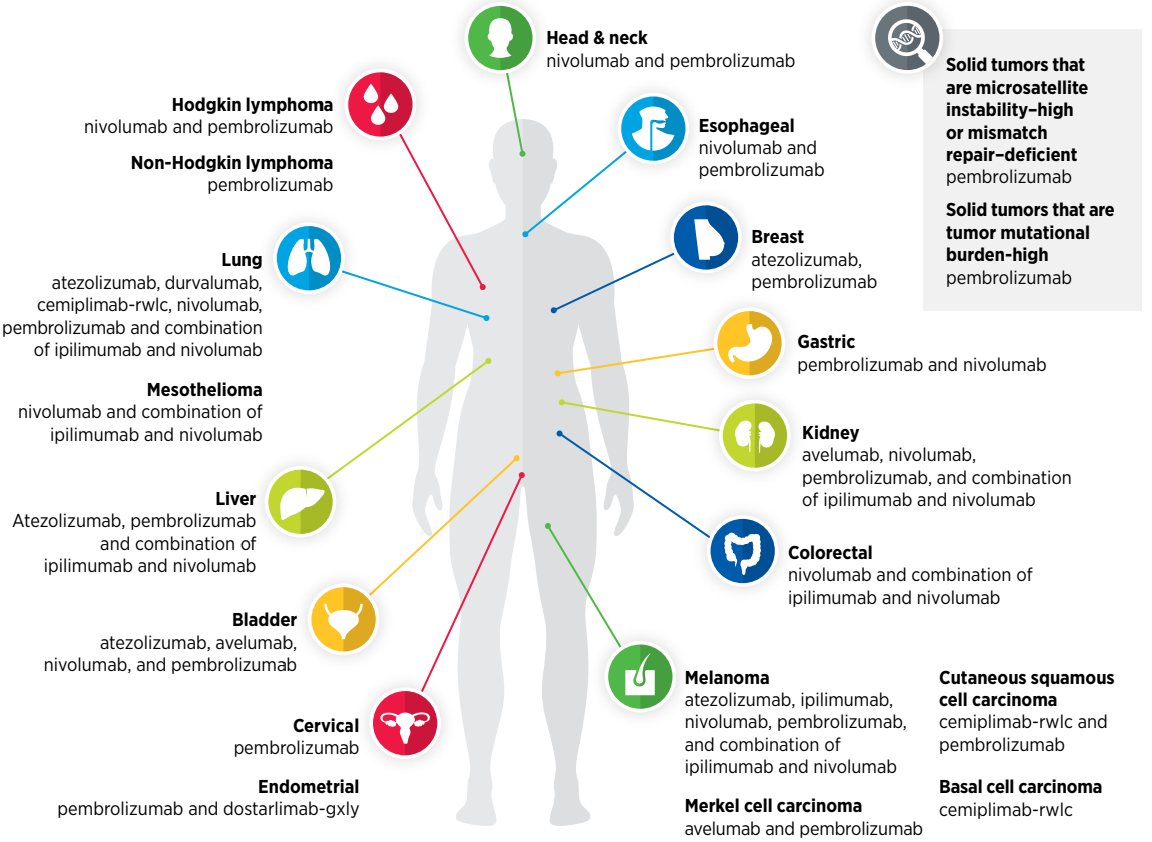
I started receiving the ipilimumab and nivolumab combination therapy in October of 2018. At that time, I had four very large tumors. The largest one was on my lung, lying on top of my liver and causing a lot of concern that it was going to infiltrate the liver. Within only three months of treatment, all the tumors started to shrink. In fact, three of them are almost nonexistent. And the fourth and largest tumor, that is on my liver, shrank to about a quarter of its original size. I had zero side effects for the first 15 months and had a very normal quality of life, which was wonderful. In January of 2021, however, I did experience some side effects. The treatment caused my immune system to attack my joints and I developed an arthritic condition that I am being treated for right now.

I truly credit the drug combination for getting me through my cancer and I sincerely hope that, with new advances in research and technology, researchers will find a cure for mesothelioma in my lifetime. I was very fortunate to have received these drugs. My experience has taught me that it is critical for patients to advocate for their own health, educate themselves the best way possible, and not settle for traditional therapies that may have been the standard of care for decades but do not have good outcomes or permit a normal quality of life. I am also a huge advocate for cancer research and clinical trials. Continued federal funding for cancer research is not just necessary but is the only way by which we will find cures for many of the cancers that currently have no effective treatments.

I am also a huge advocate for cancer research and clinical trials. Continued federal funding for cancer research is not just necessary but is the only way by which we will find cures for many of the cancers that currently have no effective treatments.

FIGURE 24

GOING DEEP WITH IMMUNE CHECKPOINT INHIBITORS



The first FDA-approved checkpoint inhibitor was ipilimumab (Yervoy), in March 2011, for metastatic melanoma. Another three-and-a-half years passed before a second checkpoint inhibitor, pembrolizumab (Keytruda), was approved, also for metastatic melanoma. Since then, another six checkpoint inhibitors have been approved by FDA and include: atezolizumab (Tecentriq), avelumab (Bavencio), cemiplimab-rwlc (Libtayo), dostarlimab-gxly (Jemperli), durvalumab (Imfinzi), and nivolumab (Opdivo). In addition, FDA has expanded the number of cancer types for which there is at least one checkpoint inhibitor approved. The broad utility of these groundbreaking immunotherapeutics is highlighted by the fact that as of July 31, 2021, 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 checkpoint inhibitors approved for treating multiple types of cancer, there are several cancer types for which there is a great selection of checkpoint inhibitors available as treatment options.

Patients with esophageal or gastroesophageal junction (GEJ) cancer have poor overall survival; only 20 percent of patients diagnosed at any stage of the disease survive five years or more (3). Furthermore, findings from a recent analysis show an alarming increase in the incidence of esophageal cancer among those younger than 50 years (108). The standard of care for esophageal cancer patients is neoadjuvant chemoradiotherapy followed by surgery to remove the tumor. Until recently, no adjuvant treatment had been established, and surveillance was the only course of action for patients who remained at high risk of recurrence after surgery. A phase III clinical trial evaluated the benefit of using the immune checkpoint

inhibitor nivolumab—previously approved in June 2020 for treatment of advanced esophageal cancer in patients who do not respond well to cytotoxic chemotherapy (467)—as adjuvant therapy to eradicate the residual cancer following surgery. The clinical trial that was used by FDA to approve nivolumab as adjuvant therapy showed that the risk of death or recurrence of cancer decreased 31 percent in patients who were treated with nivolumab following surgery when compared to patients in the control group. Moreover, the median disease-free survival of patients who underwent adjuvant therapy with nivolumab was twice as long as for those who received placebo (509). These results led FDA to approve nivolumab in May 2021 as an adjuvant therapy for esophageal and GEJ cancer patients, who had residual cancer at the time of surgery.

In April 2021, FDA approved nivolumab in combination with fluoropyrimidine- and platinum-containing chemotherapy for the initial treatment of patients with advanced or metastatic gastric cancer, GEJ cancer, and esophageal adenocarcinoma. The approval was based on data from a large clinical trial which showed that the addition of nivolumab to a chemotherapeutic regimen increased median overall survival of patients by more than two months compared to chemotherapy alone.

During the 12 months spanning this report, FDA also approved the immune checkpoint inhibitor pembrolizumab in combination with fluoropyrimidine- and platinum-containing chemotherapy to treat patients with metastatic or locally advanced esophageal or GEJ cancer whose tumor can neither be removed by surgery nor treated with chemoradiotherapy. The addition of pembrolizumab to chemotherapeutic regimens increased median overall survival of patients to more than a year, compared to less than 10 months in those who only received chemotherapy.

In May 2021, FDA expanded the use of pembrolizumab in combination with the HER2-targeted therapeutic trastuzumab and fluoropyrimidine- and platinum-containing chemotherapy for the first-line treatment of gastric or GEJ cancer patients whose tumors were metastatic or at an advanced stage and were positive for HER2, a protein frequently found on the cell surface of many types of cancer including gastric cancer. Seventy-four percent of patients who had pembrolizumab added to their treatment regimen (i.e., trastuzumab and fluoropyrimidine- and platinum-containing chemotherapy) had tumor shrinkage compared to 52 percent of those who were in the control group.

Recurrent or metastatic triple-negative breast cancer accounts for about 10-15 percent of all breast cancer and is characterized by rapid clinical progression and limited treatment options (3). During the 12 months spanning this report, FDA further expanded the use of pembrolizumab in combination with chemotherapy to treat patients who have locally recurrent or metastatic triple-negative breast cancer (TNBC) that cannot be surgically removed and whose tumors express the checkpoint protein PD-L1. The FDA also approved the PD-L1 IHC 22C3 pharmDx as a companion diagnostic for selecting patients with TNBC who are eligible for treatment with pembrolizumab. The approval was based on findings that TNBC patients, treated with a combination of pembrolizumab and chemotherapy, showed a median progression-free survival of 9.7 months, compared to only 5.6 months in the control group (510).

The remarkable benefit of checkpoint inhibitors in saving and improving the lives of patients across a broad spectrum of cancer types 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 establish whether patients who are treated with newly approved immunotherapeutics develop any common side effects, as has been recently reported for melanoma patients on adjuvant immunotherapy, and how to effectively mitigate these adverse effects (511).

Engineering Immune Cells to Eliminate Cancer

Another form of immunotherapy that has shown extraordinary success against certain types of cancer is called adoptive cell therapy or cellular immunotherapy. Adoptive cell therapy is one of the more recent approaches that 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 (512). Adoptive cell therapy is a complex multistep medical procedure. During the treatment, T cells are harvested from the patient to either expand them in number or genetically modify them in the laboratory to enhance their cancer-fighting capabilities, and then reinfused in the patient to help eliminate cancer cells. Currently, there are three types of adoptive cell therapies:

- For 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 gene that encodes a protein called a CAR. The T cells are expanded in number and infused back into the patient. The CAR modification targets the T cells specifically to the patient's cancer cells and triggers them to attack when they get there. This is the only type of adoptive cell therapy that is currently approved by FDA for treatment of different types of cancer (see sidebar on **FDA-approved CAR T-Cell Therapies**, p. 116).
- For 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 encodes a protein called a TCR. The T cells are expanded in number and infused back into the patient. The TCR modification targets the T cells specifically to the patient's cancer cells that express a particular peptide recognized by the TCR and triggers them to attack.
- For tumor-infiltrating lymphocyte (TIL) therapy, T cells are harvested directly from a patient's tumor, expanded in number in the laboratory, and infused back into the patient. Many of these T cells naturally recognize and kill the patient's cancer cells.

Because of the complex nature of the procedure, as well as the potentially life-threatening side effects of the treatment, CAR T-cell therapies are only performed at specially certified health care facilities by highly trained medical professionals. Ongoing research is focused on developing strategies that reduce the complexity of the procedure, while simultaneously increasing the benefit for the patient. One such strategy is to use frozen or "off-the-shelf" CAR T cells that are developed using T cells from donors other than the patient. The benefits of using these CAR T cells include immediate availability and the possibility to genetically modify them against multiple targets present on the cancer cell surface (513). However, potentially life-threatening side effects of using frozen CAR T cells, as well as the challenge of their rapid elimination by the patient's immune system, remain key barriers in routinely using this strategy to treat cancer and addressing these barriers is an active area of cancer immunology research (514).

The extraordinary progress toward harnessing the potential of adoptive T-cell therapy for treatment of cancer is underscored by the approval of two new CAR T-cell therapies covered in this report: idecabtagene vicleucel (Abecma) to treat relapsed or refractory multiple myeloma, and lisocabtagene maraleucel (Breyanzi) to treat relapsed or refractory large B-cell lymphoma. During the 12 months covered in this report, FDA also expanded the use of axicabtagene ciloleucel (Yescarta) to treat relapsed or refractory follicular lymphoma. These approvals bring the number of FDA-approved CAR T-cell therapies to five.

Idecabtagene vicleucel is the first FDA-approved adoptive cell therapy for multiple myeloma (see sidebar on **Two Decades of Progress Against Multiple Myeloma**, p. 91) and is great news for patients like **David Wellenstein, MD** (see p. 118). It was approved for the treatment of adult patients with relapsed or refractory multiple myeloma who have received four or more prior lines of therapy, including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 monoclonal antibody. The design of idecabtagene vicleucel is unique because it is directed against the protein B-cell maturation antigen (BCMA) on cancer cells, compared to prior CAR T-cell therapies approved by FDA that were directed against the protein CD19 on cancer cells (464). Expression of BCMA is largely restricted to plasma cells, which are blood cells that make antibodies to protect against infections (434), and is much higher in myeloma cells compared to normal plasma cells (462). Among the 128 patients participating in the clinical trial who received idecabtagene vicleucel, the overall response rate was 73 percent, and 33 percent of patients achieved complete response (see **Table 6**, p. 87), meaning that cancer was no longer detectable. An estimated 65 percent of those with complete response maintained this response for at least one year (515). The use of BCMA marks a key milestone in CAR T-cell therapy because it provides options to develop CAR T cells that are more specific to a cancer type and can potentially reduce some of the serious side effects associated with CAR T-cell therapies.

The second newly approved CAR T-cell therapy is lisocabtagene maraleucel, which is directed against CD19 and induces cell death in CD19-expressing cancer cells. In February 2021, FDA approved lisocabtagene maraleucel for the treatment of adult patients with relapsed or refractory large B-cell lymphoma who have received two or more lines of systemic therapy, including patients with diffuse large B-cell lymphoma (DLBCL) not otherwise specified, high-grade B-cell lymphoma, primary mediastinal large B-cell lymphoma, and follicular lymphoma.

The FDA approval of lisocabtagene maraleucel was based on data from a clinical trial evaluating efficacy of the treatment in 192

THE FDA-APPROVED CAR T-CELL THERAPIES

As of July 31, 2021, only one type of adoptive cell therapy, the chimeric antigen receptor (CAR) T-cell therapy, is approved by the U.S. Food and Drug Administration. There are five distinct CAR T-cell therapies to treat different cancer types, as listed below by the year they were first approved by FDA:

2021

Idecabtagene vicleucel (Abecma) to treat adult patients with relapsed or refractory multiple myeloma.

Lisocabtagene maraleucel (Breyanzi) to treat adult patients with certain types of B-cell lymphoma.

2020

Brexucabtagene autoleucel (Tecartus) to treat patients with relapsed or refractory mantle cell lymphoma.

2017

Tisagenlecleucel (Kymriah) to treat adults with certain types of B-cell lymphoma and young adult patients up to age 25 with certain types of lymphoblastic leukemia.

Axicabtagene ciloleucel (Yescarta) to treat adult patients with certain types of B-cell lymphoma.

These treatments have transformed the lives of many pediatric and adult patients with cancer.

adult patients with relapsed or refractory large B-cell non-Hodgkin lymphoma who had received at least two previous therapies. Of these patients, 54 percent had minimal or no detectable lymphoma remaining following treatment with lisocabtagene maraleucel and another 19 percent achieved a partial response. Of 104 patients who achieved the best overall response to the treatment, the cancer remained undetectable or at reduced levels for at least nine months in 62 percent of patients (516).

Treatment with lisocabtagene maraleucel can cause severe and potentially life-threatening adverse effects. One of the most concerning is cytokine-release syndrome (CRS), an inflammatory response to the modified T cells that can rapidly cause organ dysfunction and/or failure, and neurotoxicity. Because of the potential serious side effects, FDA has approved lisocabtagene maraleucel with a risk evaluation and mitigation strategy under which health care facilities administering the treatment are required to be specially certified to recognize and manage CRS and nervous system toxicities.

During the 12-month period covered by this report, FDA also expanded the use of a previously approved CAR T-cell therapy, axicabtagene ciloleucel (Yescarta), for adult patients with relapsed or refractory follicular lymphoma (FL) who have received two or more lines of systemic therapy. The FDA's decision was based on clinical trial results showing that axicabtagene ciloleucel therapy eliminated all signs of cancer in 60 percent of patients within one month of the treatment.

Ongoing research is focused on identifying proteins that are preferably present only on the surface of cancer cells and can be used to develop CAR T-cell therapies that are more specific to the type of cancer against which they are being used. These approaches, such as development of a CAR that targets both CD19 and CD22 proteins present on the cell surface in B-cell lymphoma thereby increasing specificity against cancer cells (517), will ensure that there are minimal adverse side effects for patients treated with these immunotherapeutics.

Unleashing the Body's Defense System Against Cancer

One class of immunotherapeutics to treat cancer works, in part, by helping immune cells find cancer cells more effectively (see **Cell Lysis Mediators** in **Supplemental Table 2**, p. 185). These immunotherapeutics use a mechanism, called antibody-dependent cellular toxicity (ADCC), to direct immune cells to the tumor, where immune cells kill the target cancer cells. During the 12-month period covered in this report, FDA approved two new immunotherapeutics—naxitamab-gqgk (Danyelza) and margetuximab-cmkb (Margenza)—that invoke ADCC to destroy cancer cells.

In December 2020, FDA approved margetuximab-cmkb in combination with chemotherapy for the treatment of adult patients with metastatic HER2-positive breast cancer who have received two or more prior HER2-targeted treatments, at least one of which was for metastatic disease. Margetuximab-cmkb is an antibody that targets HER2, a protein commonly present in high concentrations on the surface of certain types of aggressive breast cancer. Once bound to HER2 protein, margetuximab-cmkb inhibits tumor growth and is designed to enhance recruitment of immune cells to kill cancer cells (518). The FDA's decision was based on results of a phase III randomized clinical trial (519). About 22 percent of patients treated with a combination of margetuximab-cmkb and chemotherapy responded to the treatment, compared to 16 percent of those treated with a combination of chemotherapy and another anti-HER2 targeted therapeutic trastuzumab (Herceptin). Patients in the margetuximab-cmkb treatment group also showed a modest increase in the length of time when the tumor did not progress (about six months versus five months in the trastuzumab treatment group). HER2-positive breast cancer is more aggressive and more likely to return than HER2-negative breast cancer (520). Even a modest benefit from new immunotherapeutics such as margetuximab-cmkb is a positive step toward improving the lives of patients with HER2-positive metastatic breast cancer.

Neuroblastoma, although a rare cancer, is the most common cancer type in infants who are less than one year old. It accounts for roughly six percent of all childhood cancers. Neuroblastoma is a particularly devastating type of cancer because, in about two thirds of the cases, it has already spread to the lymph nodes or to other parts of the body at the time of diagnosis (3). Most common treatments for neuroblastoma—depending on the extent to which the disease has progressed—include surgery, chemotherapy, and radiation therapy. Only 40-50 percent of patients diagnosed with high-risk neuroblastoma—the form of neuroblastoma that cannot be removed surgically—live five years or more after diagnosis (3), underscoring an unmet need to develop effective therapeutics against it (521). In November 2020, FDA granted approval to naxitamab-gqgk (Danyelza) in combination with granulocyte-macrophage colony-stimulating factor (GM-CSF), an immune-system boosting agent, for children one year of age and older and adult patients with relapsed or refractory high-risk neuroblastoma in the bone or bone marrow who have shown a partial response, minor response, or stable disease to prior therapy. Naxitamab-gqgk joins dinutuximab (Unituxin) to become the second immunotherapeutic approved by FDA to treat patients with high-risk neuroblastoma. Similar to dinutuximab, naxitamab-gqgk also binds to GD2, a lipid-carbohydrate hybrid molecule, that is present on the surface of neuroblastoma cells (522). Naxitamab-gqgk binds to GD2 and flags neuroblastoma cells for immune cells which upon binding to another part of naxitamab-gqgk are triggered to destroy the cancer cell. In one of the two clinical trials evaluating efficacy of naxitamab-gqgk, the overall response rate (see **Table 6**, p. 87) among 38 patients treated with naxitamab-gqgk was 34 percent, and 23 percent of those who responded maintained the response for at least six months. In the second trial, the overall response rate among 22 patients who received the treatment was 45 percent, and 30 percent of those who responded maintained the response for at least six months. Long-term evaluation of patients who received the treatment, as well additional independent clinical studies, will be necessary to determine whether naxitamab-gqgk treatment also improves overall survival and quality of life for patients with high-risk neuroblastoma.

DAVID WELLENSTEIN, MD AGE 74 | Sauquoit, New York

Reclaiming the Joys of Retirement Thanks to CAR T-Cell Therapy

Six years ago, I felt one or more ribs break when I took a swing with my golf club. X-rays and follow-up scans led to the diagnosis of advanced multiple myeloma. Over the next year and a half, I went through multiple treatment regimens and while initially I responded positively to each treatment, my cancer markers would start to rise after a while. The treatments also resulted in severe side effects that significantly impacted my quality of life. Then, about three years ago I participated in a clinical trial for idecabtagene vicleucel (Abecma). Since then, my cancer markers have gone down to zero and the PET-CT scans show no sign of active cancer. I am enjoying my hobbies working with wood and metal at my dream shop and spending time with my family.

My journey with cancer started about six years ago. I was 68. I'm a radiologist. At the time, my wife and I were planning our retirement. I had been encouraged to take up golfing as a new hobby while spending time in Florida and was told that the experience is quite different here in the Northeast because the grass is different. So, when I got back home, I decided to take a swing on my lawn to see. The grass indeed was different. The club got caught a bit and I had a sudden pain in my left chest. I knew that I had fractured at least one rib. After a few days, I was still in pain and went to my hospital to take a chest X-ray. It was a Saturday and since there were no other radiologists there, I took a peek myself. I found three rib fractures and, as I was taking one last look, I noticed multiple tiny holes throughout my skeleton. I immediately knew what it was. As radiologists, we don't see it often, but it was the certain pattern of multiple myeloma and it appeared to be quite advanced. I was shocked. I had to sit there for a few minutes to regain my composure. The following week I saw an oncologist who agreed with my diagnosis and recommended a bone marrow biopsy, CT scan and a PET scan to confirm and stage the disease.

We laid out a plan for my treatment. My first regimen consisted of three drugs: a targeted therapeutic, bortezomib (Velcade), an immune modulator, lenalidomide (Revlimid), and a steroid, dexamethasone (Decadron). I received these treatments for three weeks and it looked like I was making marked improvement. The cancer marker numbers were dramatically down. We continued with this treatment with a three week on and one week off schedule and the cancer markers continued to decline. However, I developed some serious side effects. I developed severe pain (neuropathy) in both legs to a point that I had to use a walker. The symptoms were getting worse and began to affect my bladder. As a result, we had to taper off my treatment for a while. Unfortunately, as soon as I went back on my old regimen the side effects returned. This was a significant challenge and I had to switch to a different treatment regimen. Over the next two years I went through nearly eight different combinations of anticancer agents. However, the neuropathy continued to be a problem. At this time upon my oncologist's recommendation, I sought treatment at the Dana-Farber Cancer Institute. There, I was treated with several newer chemotherapy regimens. Unfortunately, these treatments always seemed to work at first, the marker numbers would come down but then inevitably, after a month or two, they would start to rise again.

As we were running out of options, my oncologist at Dana-Farber discussed the possibility of getting into a clinical trial that was testing a new CAR T-cell therapy in patients with refractory multiple myeloma. I thought it was a very intriguing approach and decided to enlist. I had to wait for a few months but eventually had the chance to enroll in the trial. The CAR T treatment was quite a process. They had to harvest T cells from my own blood, modify them in a laboratory, expand them in large numbers, and infuse them back into me. I had the process done twice since we had to stop my first treatment after I experienced some confusion which is one of the known side effects of the therapy. During the second round, I received the maximum possible number of the altered T cells that could be administered.

Since my last infusion about three years ago, we have been monitoring my disease through bone marrow biopsies as well as complete blood workups. My cancer marker number has gone down to zero and the PET-CT scans show no sign of active myeloma. The side effects have also been stabilized. These days I am back at my shop doing a lot of wood turning and blacksmithing and most importantly spending time with my grandchildren making birdhouses. I can't emphasize enough the importance of funding cancer research because I've experienced firsthand the incredible impact science-driven advances can have on lives.

I can't emphasize enough the importance of funding cancer research because I've experienced firsthand the incredible impact science-driven advances can have on lives.

SUPPORTING CANCER PATIENTS AND SURVIVORS

In this section, you will learn:

- As of 2019, more than five percent of the U.S. population is living with a history of cancer.
- Each person diagnosed with cancer faces a unique set of challenges; 25 percent of cancer survivors report poor physical health and 10 percent report poor mental health, both adversely affecting quality of life.
- Researchers are exploring ways to utilize healthy behaviors, palliative care, psycho-oncology, and other evidence-based strategies to improve survival and quality of life for patients with cancer.
- Additional research is pivotal to tailor new technologies and intervention strategies for coordinated care that improves the quality of life and meets the personalized needs of cancer survivors and caregivers from different age groups.

Discovery science-driven clinical breakthroughs across the continuum of cancer care are saving lives and helping individuals live longer and fuller lives after a cancer diagnosis. In 2019, the most recent year for which such data are available, cancer survivors accounted for more than five percent of the entire U.S. population, a remarkable improvement since 1971, when cancer survivors made up only 1.4 percent of the U.S. population (**Figure 25**, p. 121). Thanks to the dedication of countless individuals across all sectors of health care and policy, cancer survivors are projected to account for nearly seven percent of the U.S. population by 2040.

According to the National Cancer Institute (NCI), a person is considered a cancer survivor from the time of cancer diagnosis through the balance of his or her life. While a person is considered a survivor from the time of cancer diagnosis through the remainder of life, not everyone identifies or agrees with this term. Each person who is diagnosed with cancer has a unique experience. These experiences range from successful treatment and living cancer free for the remainder of life, with or without adverse effects of treatment, to living with cancer and any effects of treatment for the remainder of life. Furthermore, as our understanding of cancer survivorship increases, there is a growing appreciation of its multifaceted

THE HONORABLE
Richard Shelby

U.S. Senator for Alabama

Vice Chairman, Senate Appropriations Committee

"Cancer research is critical to our ability to prevent, treat, and cure all forms of cancer. As a cancer survivor, I have supported funding for this important cause for many decades and plan to continue backing good investments in medical research that can save lives."

THE HONORABLE
Mark DeSaulnier

U.S. Representative for California's 11th District

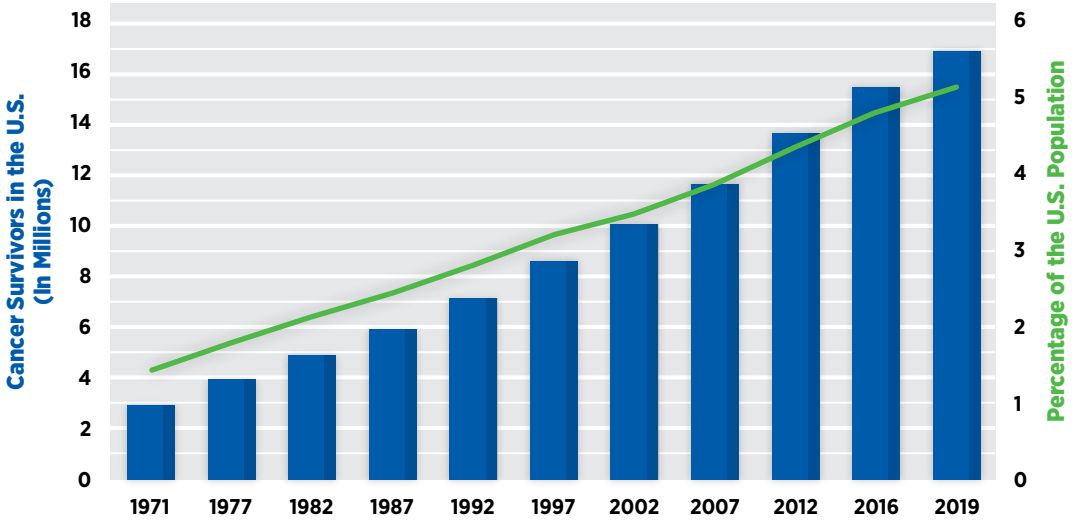
Co-Chair, Cancer Survivors Caucus

"As a survivor of chronic lymphocytic leukemia, I know firsthand the importance of federal investments in cancer research and the difference it can make for countless Americans. This research has allowed me to count myself as a survivor. Through my work as founder of the Congressional Cancer Survivors Caucus, I've pushed for increased research funding so others may have the same shot and am proud that since 2015, we've increased funding to the National Cancer Institute by over $1.5 billion. Thanks to these investments, the medical and research community have made tremendous advancements, and we must continue that fight until cancer is a disease of the past."

FIGURE 25

NATIONAL CANCER ACT
50 YEARS
1971-2021

50 YEARS OF SAVING LIVES



The number of cancer survivors in the United States, shown in millions (blue bars), has increased steadily from less than two percent of the U.S. population in 1971 to more than five percent of the U.S. population in 2019 (green line).

impact on family members, friends, and caregivers of those diagnosed with cancer (523).

Challenges Faced by Cancer Survivors

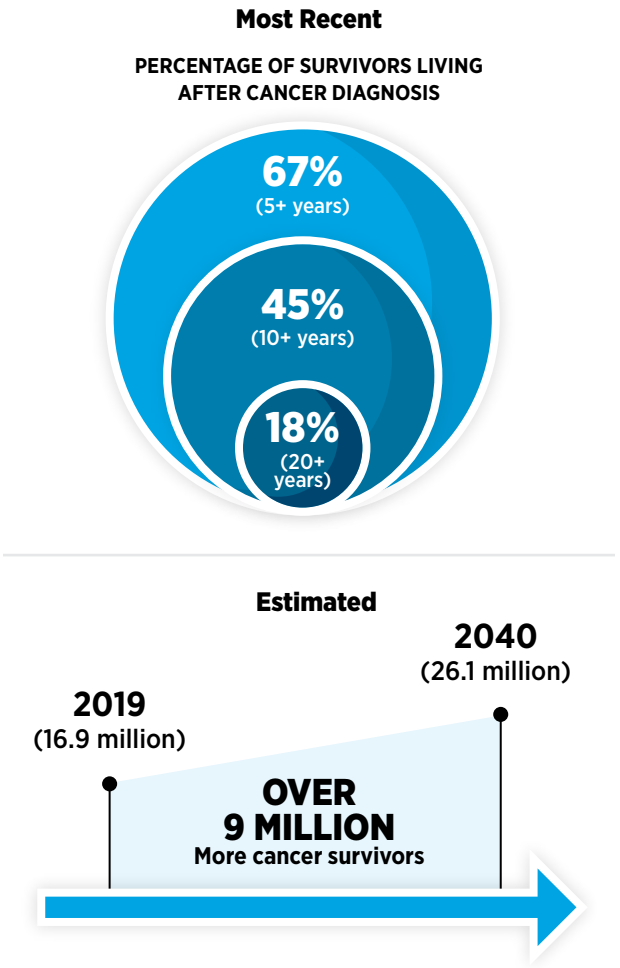
Depending on the type and stage of cancer, as well as the age at which an individual is diagnosed, cancer survivorship can encompass a wide range of unique experiences of living with, through, and beyond cancer (see sidebar on **Phases of Cancer Survivorship**, p. 123).

Physical, psychosocial, and financial stresses can deprive individuals diagnosed with cancer of meaningful life experiences regardless of which phase of survivorship the individual is experiencing. These challenges can also disrupt the lives of family members, friends, and other caregivers. It is important to note that the challenges discussed here are interrelated and may collectively contribute to the burden of cancer faced by cancer patients and survivors. For example, limited physical mobility because of cancer treatment and/or financial difficulties of paying for medical bills can lead to distress and/or depression.

PHYSICAL CHALLENGES

Individuals diagnosed with cancer can face both acute and chronic symptoms from the cancer itself, as well as from the treatment. Both short- and long-term symptoms experienced by cancer survivors can be debilitating. Before and during cancer treatment, individuals may experience a variety of symptoms, including hair loss, pain, swelling of arms and legs (lymphedema), joint pain (arthritis), loss of sleep, nausea, vomiting, and loss of 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 (including peripheral neuropathy), cognitive decline, premature aging, infertility, and sexual dysfunction as well as development of secondary cancers (see sidebar on **Phases of Cancer Survivorship**, p. 123). For example, among more than 1.5 million adults who were diagnosed with cancer between 1992 and 2011 and survived five years or more, male and female survivors were at a 45 and 33 percent higher risk compared to risks in the general population, respectively, of dying from a new type of cancer (182). Ongoing research is aimed at understanding the risk

U.S. CANCER SURVIVORSHIP AT A GLANCE



factors that make patients susceptible to these late effects and ways to prevent them. Emerging evidence suggests that an active and healthy lifestyle can play an important role in coping with deleterious effects of cancer treatment, such as cardiopulmonary dysfunction (see **Promoting Healthy Behaviors**, p. 125). Furthermore, palliative care—a specialized type of care that provides an additional level of support for cancer survivors throughout their experience with cancer—can significantly improve quality of life (see **Palliative Care**, p. 126).

PSYCHOSOCIAL CHALLENGES

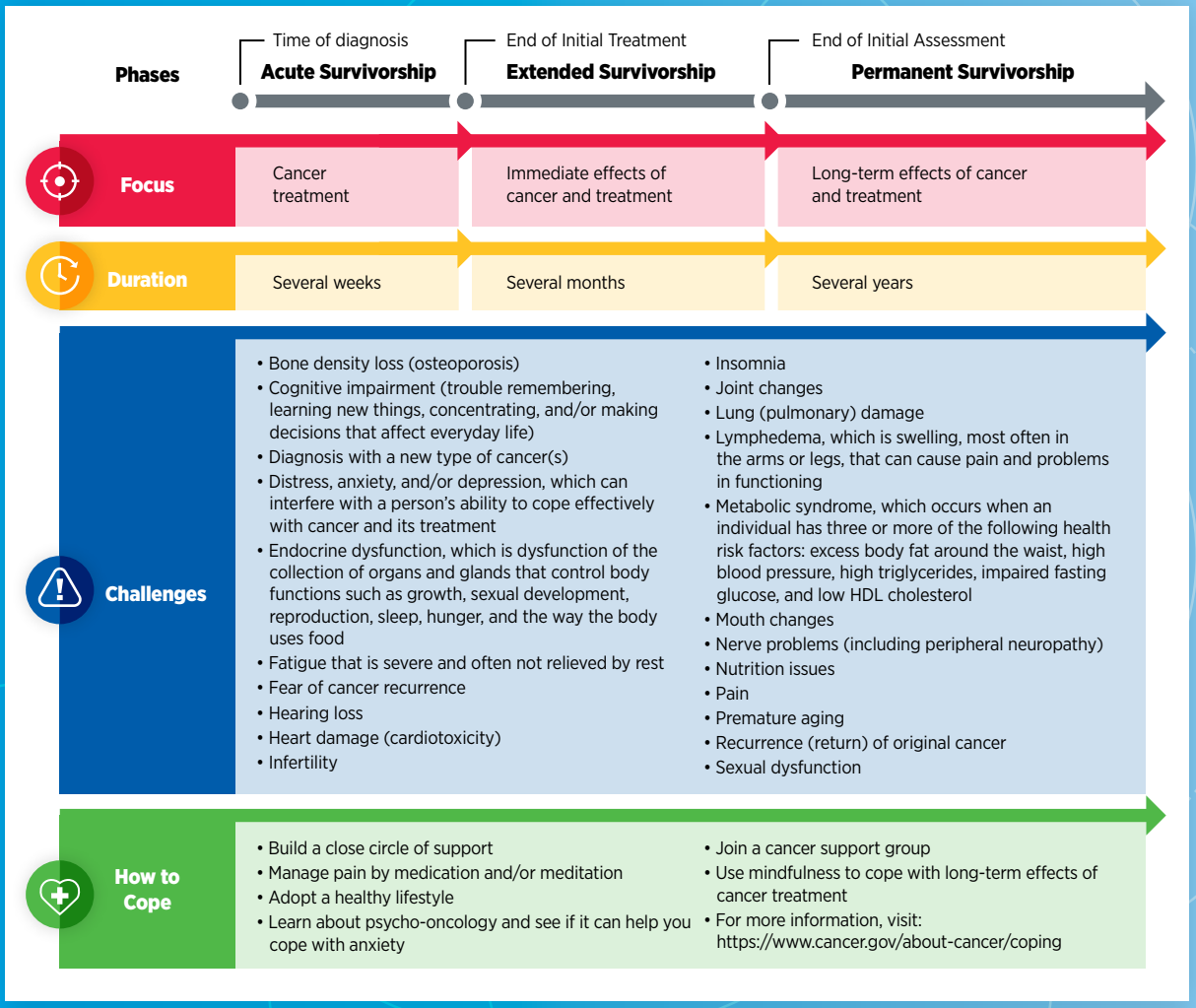
Cancer diagnosis and treatment pose serious challenges to a person's mental and emotional health. Anxiety of cancer returning or concern of being diagnosed with a new type of cancer even after successful cancer treatment can lead to distress and/or depression. A recent study found that survivors of stomach cancer had anxiety that was associated with fear of cancer recurrence (524). Similarly, individuals who are under active surveillance after diagnosis of early-stage cancer that does not require therapy also face the anxiety and distress of cancer eventually progressing. For example, patients diagnosed with an early-stage prostate cancer who were under active surveillance often reported feeling anxious, depressed, uncertain and/or hopeless (525). Impairment of cognitive skills due to cancer treatment, such as loss of memory, decline in the ability to learn new things, trouble concentrating, and/or indecisive attitude, can affect everyday life. Studies have shown that an estimated 10-30 percent of cancer patients exhibit detectable cognitive impairment even before cancer treatment, likely due to the distress and anxiety caused by the cancer diagnosis. Approximately 15-35 percent of cancer patients reported diminished cognitive functions several months after completion of cancer treatment (526). Late effects of cancer diagnosis and treatment are yet another source of anxiety and distress among long-term survivors of cancer. A recent study found that many survivors of prostate cancer reported a feeling of abandonment and lack of psychosocial and informational support to address persisting treatment-induced side effects (527). Increased understanding of the far-reaching impact of cancer on a person's life has spurred the field of psycho-oncology, an interdisciplinary approach to providing support for cancer patients confronting numerous behavioral, emotional, psychological, and social challenges throughout the different stages of survivorship (see **Psycho-oncology**, p. 127).

FINANCIAL CHALLENGES

Financial hardship, or financial toxicity, associated with cancer treatment and management poses a key challenge to the mental and emotional health of the individual diagnosed with cancer, as well as that of immediate family members who may depend on the cancer survivor for their livelihood. Accruing evidence points to the many ways by which financial hardship affects cancer survivors and their dependents. In one recent survey of patients with gynecologic cancers, nearly half of the participants reported that they faced moderate (such as borrowing money) to severe (such as unable to pay for prescription medication) financial hardship because of cancer treatment and management (528). Another study examining the financial impact on survivors 70 years or older who had advanced-stage cancer found that 18 percent of the participants experienced financial toxicity and higher levels of depression, anxiety, and distress (529). Cancer diagnosis can also adversely

In the United States, **annual costs associated with metastatic breast cancer** among women will total $152.4 billion in 2030—**nearly two and a half times** the estimate of 2015 costs—due to an increase in cases among younger women (531).

PHASES OF CANCER SURVIVORSHIP



Although all cancer survivors face challenges, survivors of cancer diagnosed during childhood, adolescence, and young adulthood (from ages <1 to 39) are particularly at risk for severe long-term and late effects. The Children's Oncology Group's "Long-Term Follow-Up Guidelines for Survivors of Childhood, Adolescent, and Young Adult Cancers" 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.

affect employment, further exacerbating financial hardship. According to one study, financial hardship was twice as likely among women who had to stop working completely or reduce work hours because of a breast cancer diagnosis (530).

UNIQUE CHALLENGES FACED BY CHILDREN, ADOLESCENTS, AND YOUNG ADULTS WITH CANCER

Coping with the adverse effects of cancer is even more challenging for those diagnosed during childhood, adolescence, and young adulthood (i.e., individuals from ages less than one year to 39 years) (532). This period in life is associated with major changes at personal, social, and emotional levels. Many young adults are only starting their journey to professional careers. A cancer diagnosis during this phase of life can irrevocably change their personal and occupational trajectories (533). Cancer survivors in this group are at a greater risk of developing additional medical conditions, such as stroke, secondary cancers, and neurodegenerative defects, compared to the general population. This risk can increase further depending upon the type of treatment they

received. A recent study performed a 10-year follow-up of nearly 7,000 adolescents, and young adults (AYA), who had survived two years or more after cancer diagnosis, for the presence of medical conditions, including cardiovascular issues, hypertension, diabetes, and pulmonary diseases. Researchers found that 40 percent of AYA who were cancer survivors had two or more comorbidities compared to those without cancer (534). According to a recent study, 32 percent of AYA women experienced disruption in their employment status (left or lost job or had to reduce their work hours) after they were diagnosed with cancer (535). Because of the unique challenges faced by younger individuals who are diagnosed with cancer, the Children's Oncology Group has developed guidelines to help standardize and improve the lifelong follow-up care of these individuals (536).

CHALLENGES FACED BY RACIAL AND ETHNIC MINORITIES AND OTHER UNDERSERVED POPULATIONS

Cancer survivors who belong to certain underserved segments of the U.S. population face additional challenges while coping with the cancer burden, a collective term to describe varied needs of a cancer survivor throughout the cancer experience. Numerous disparities, stemming largely from systemic and structural racism and discrimination, disproportionately and adversely affect the health and quality of life of cancer survivors from underserved population groups. As an example, African American women diagnosed with breast cancer were less likely to receive a timely surveillance mammogram compared to whites (537) (see sidebar on **Disparities in Health and Quality of Life After a Cancer Diagnosis**).

The COVID-19 pandemic has further exacerbated the numerous challenges faced by cancer survivors (see sidebar on **Impact of the COVID-19 Pandemic on Cancer Survivors**, p. 125). Although long-term effects of the pandemic on cancer survivors will be clearer with time, preliminary indications point to the impacts of the pandemic that range from worsening of physical, psychosocial, and financial well-being to exploration of new opportunities such as adapting to technology-based means of health care delivery.

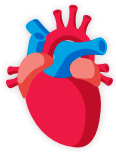
Improving Quality of Life and Outcomes for Cancer Survivors Across the Continuum of Cancer Care

The NCI defines quality of life as the overall enjoyment of life measured by aspects of an individual's sense of well-being and ability to carry out activities of daily living. Because the impact of cancer diagnosis and treatment on a person is multifaceted and far-reaching (see **Challenges Faced by Cancer Survivors**, p. 121), the notion of quality of life throughout cancer survivorship (see sidebar on **Stages of Cancer Survivorship**, p. 123) is also multidimensional and includes physical, psychosocial, emotional, and financial well-being. As more cancer survivors are living longer, the concept of quality of life

DISPARITIES IN HEALTH AND QUALITY OF LIFE AFTER A CANCER DIAGNOSIS

Several segments of the U.S. population have been found to be disproportionately affected by the health complications related to cancer and cancer treatment that adversely affect health and quality of life after a cancer diagnosis. Examples of these disparities include:

Food insecurity, such as worrying about running out of food, skipping of meals, and being hungry without eating, was **nearly three times more likely among Hispanic survivors** of thyroid cancer compared to non-Hispanics (539).



Excess heart age, which is a measure of cardiovascular damage and the risk for a heart attack, was **9.2 years higher** among women cancer survivors ages 50 to 59 who were **non-Hispanic African American** compared to those who were non-Hispanic white (540).

Long-term survival at 15 years postdiagnosis was **significantly better** among adolescent and young adult (AYA) cancer survivors who had **private insurance** compared to those who had public insurance (89 versus 62 percent, respectively) (541).

High financial stress, such as lifestyle-altering changes, was **more than 12 times higher** among cancer survivors ages 35-44, when compared to those who were age 65 or older (542).

IMPACT OF THE COVID-19 PANDEMIC ON CANCER SURVIVORS

The COVID-19 pandemic has negatively affected many aspects of everyday life, including health and quality of life of cancer survivors. Examples of how the COVID-19 pandemic has impacted the lives of cancer survivors include:

77% and **27%**	According to a survey of cancer survivors conducted between March and April 2020, 77 percent of participants reported **anxiety about being at a higher risk of serious health** impact if infected with COVID-19; 27 percent of cancer survivors reported **anxiety about financial impact** of the pandemic (543).
50%	50 percent of caregivers of childhood cancer survivors surveyed between April and May 2020 reported **delays or cancellations of follow-up appointments** after the cancer treatment (544).
59%	59 percent of cancer survivors surveyed between July and October 2020 reported **reduced social support from family and friends** (545).
32%	32 percent of cancer survivors surveyed in June 2020 reported an **adverse impact of the pandemic on their physical health**, such as less physical activity, weight gain, and increased pain (546).

has become an integral part of the cancer care continuum as well as a focus of intense research.

Advances in treating cancer based on specific genetic mutations or biomarkers are improving long-term survival of cancer patients (546,547). Today, many cancer survivors are experiencing improved quality of life and living their lives as active members of society. This success is reflected in the cancer experience of **Zach Witt**, now a 16-year-old high school student, who was treated with a molecularly targeted therapeutic when he was diagnosed with a certain type of lymphoma as a 9-year-old (see p. 104).

Longer survival among cancer patients following treatment with molecularly targeted therapeutics and immunotherapeutics also comes with the possibility of long-term or late effects from these treatments (548). For example, according to a recent report, poly ADP-ribose polymerase (PARP) inhibitors, a class of molecular therapeutics that target the DNA repair pathway in cancer cells, more than doubled the risk of myelodysplastic syndrome and acute myeloid leukemia among recipients when compared to the placebo treatment (549). Another recent study showed that 43 percent of melanoma patients who were treated with immunotherapeutics developed long-term immune-related side effects (511). These findings emphasize the need to carefully monitor the adverse side effects of newer treatments such as targeted therapeutics and immunotherapeutics and to identify ways to help cancer survivors cope with short-term, long-term, and late effects of their treatments. Researchers are exploring various strategies to improve the survival and quality of life of cancer survivors. Some of these approaches are discussed below.

PROMOTING HEALTHY BEHAVIORS

Certain lifestyle changes can significantly improve quality of life for cancer survivors. These include eliminating tobacco use, adopting a healthy diet, increasing physical activity, and reducing alcohol consumption. Accruing evidence suggests that continued adherence to unhealthy lifestyle behaviors increases the risk of secondary cancers and overall mortality and decreases overall health and quality of life among cancer survivors (550).

Tobacco use is causally linked to significantly increased risk of developing at least 18 different types of cancer (see **Preventing Cancer: Identifying Risk Factors**, p. 36). Smoking tobacco is also associated with worse outcomes after a cancer diagnosis (551). A recent study found that smoking cessation among cancer survivors decreased their risk of dying because of cancer by 25 percent (552). Among cancer survivors diagnosed between 2000 and 2017, more than 24 percent were smokers at the time of first cancer diagnosis. Encouragingly, the likelihood of cigarette smoking cessation among cancer survivors increased with the year of cancer diagnosis from 2000 to 2017 (553). Another study found that successful cessation of cigarette

smoking among survivors of bladder cancer was more frequent around the time of initial diagnosis (554). These promising findings underscore the opportunity to educate cancer survivors about how cigarette smoking can negatively impact cancer treatment and survival. There is also an opportunity to develop new and innovative strategies such as those based on digital health, e.g., internet and smartphone applications, that promote smoking cessation among cancer survivors. There is preliminary evidence that using smartphone applications among cancer survivors for cessation of smoking can be effective (555). Additional research is underway to develop evidence-based approaches that use a range of modern means of communication to encourage smoking cessation among cancer survivors (556).

An active lifestyle that includes exercising regularly and participating in outdoor activities is beneficial to everyone (see **Preventing Cancer: Identifying Risk Factors**, p. 36). An active lifestyle is especially valuable for cancer survivors because it can help mitigate numerous physical and psychosocial challenges they experience. As an example, prostate cancer survivors who participated in an exercise program reported significant improvements in their physical, mental, and emotional health (557). Similarly, breast cancer patients who maintained an active lifestyle after cancer diagnosis and through the course of treatment had reduced recurrence of cancer, decreased mortality, and improved overall survival (558,559). Maintaining a healthy lifestyle is also associated with reducing the risk of cardiovascular disease and improving bone health among cancer survivors (560,561). Researchers are examining additional ways to encourage cancer survivors to maintain an active lifestyle after diagnosis. One study found that cancer survivors exercise at a higher intensity during outdoor compared to indoor exercise sessions (562). The popularity of fitness trackers has given health care providers additional tools to implement innovative strategies that capitalize on the benefits of an active lifestyle for cancer survivors. Early studies have shown that the use of fitness trackers can reduce sedentary behavior and increase moderate-to-vigorous-intensity physical activity, which is associated with improved mental health and performance (563). Use of digital health approaches is especially effective among AYA, a population group that is already adept in applying technology-based solutions across various aspects of their lives. In one recent study, cancer patients ages 15 to 29 were offered a wearable fitness tracker and a tablet at the time of cancer diagnosis to track their physical activity. Those who participated in the study showed increased physical activity and improvements across multiple measures of quality of life (564). Ongoing studies are further investigating the benefit of such approaches for improving management of short-term, long-term, and late effects of living with cancer (565).

Eating a balanced diet that includes the major food groups—vegetables, whole grains, fruits, and protein—is central to developing and maintaining a well-rounded healthy lifestyle. Healthy eating habits improve quality of life for cancer survivors. One study found that adherence to a healthy diet was associated with reduced risk of cancer recurrence or death among long-term breast cancer survivors (566). Unfortunately, there are concerning reports that indicate a lack of adherence to dietary recommendations among cancer survivors (567,568). A recent study found that alcohol consumption, which is linked with elevated risk for several cancer types, was increased among survivors of head and neck cancer within two years of diagnosis (569). Notably, the lack of easily understandable information on healthy eating and absence of support for changing dietary behaviors have been reported as two major barriers to adopting a healthy diet among cancer survivors (570). These findings highlight the urgent need to effectively communicate and promote healthy dietary behaviors among individuals with a history of cancer. Researchers are using fitness trackers, smartphone applications, and other innovative approaches to inform and encourage cancer survivors about the long-term advantages of a healthy diet for an enhanced quality of life (571).

The positive impact of maintaining healthy behaviors has prompted many health-related federal agencies and cancer-focused professional societies to offer comprehensive guidelines that help cancer survivors adopt a long-lasting healthy lifestyle (572–575).

PALLIATIVE CARE

Palliative care is a multidisciplinary approach to providing optimized quality of life for people with cancer, as well as their families and caregivers (see sidebar on **What Is Palliative Care?**, p. 127). Palliative care aims to alleviate the adverse effects of cancer diagnosis and treatment and addresses the psychological, social, and spiritual challenges faced by cancer survivors. Individuals with cancer can receive palliative care throughout their experience with cancer, beginning at diagnosis and continuing through treatment, follow-up, survivorship, and end-of-life decisions.

Integration of palliative care during the early stage of a person's cancer experience can significantly improve quality of life. Multiple studies have shown that palliative care leads to a better management of symptoms resulting from cancer and/or its treatment, decreases depression and anxiety, improves quality of life for both cancer survivors and their caregivers, and results in longer survival (576–579). Ongoing studies are further investigating different methods to help cancer survivors cope with various adverse effects of cancer diagnosis and treatment. In an ongoing clinical trial that included cancer survivors with chronic musculoskeletal pain, electroacupuncture—a form of acupuncture where a small electric current is passed between pairs of acupuncture needles—reduced the pain twice as much as usual care in the 12-week period spanning the treatment (580). Findings from another ongoing clinical trial showed that high-dose radiation therapy, called stereotactic body radiation therapy, or SBRT, was highly effective in relieving the pain experienced by some patients with painful spinal metastases from advanced cancer (581). About a third of cancer patients in

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 can be 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; and
- Spiritual challenges.

the study who received radiation therapy for spinal metastases did not experience pain up to six months after treatment, compared to only about 15 percent of people who received conventional external beam radiation therapy to treat the pain (581). These findings are highlighting the importance of integrating palliative care throughout the continuum of clinical cancer care. As of 2018, 95 percent of the NCI-designated cancer centers had outpatient palliative care clinics. In contrast, only 40 percent of non-NCI-designated cancer centers had outpatient palliative care clinics (582). NCI-designated cancer centers were also more likely that non-NCI-designated cancer centers to have fellowships in palliative care for medical trainees (87 vs 30 percent) and research programs focused on palliative care (58 vs 15 percent) (583). These findings highlight the opportunities to further improve palliative care programs that can effectively assist cancer survivors and caregivers at any stage during their experience with cancer (584).

In addition to the investments in institutional infrastructure for palliative care delivery, it is equally important to raise awareness of the numerous benefits of palliative care among cancer survivors and their caregivers. According to recent findings, 66 percent of cancer survivors had never heard of palliative care, and only 17 percent knew enough about palliative care to explain it to someone else (585). In a pilot study, knowledge of palliative care increased by 83 percent among cancer patients when they received a multimedia intervention providing knowledge and reassurance about the purpose and nature of palliative care. Researchers also found that patients' perception of what palliative care was improved by nearly 19 points (586). As researchers develop additional strategies to improve the uptake of palliative care, it would be vital to ensure equitable access to any such approaches for all patient populations.

PSYCHO-ONCOLOGY

Psycho-oncology is an interdisciplinary subspeciality within the cancer care continuum that aims to address the physical, behavioral, emotional, and psychosocial distress that arises for cancer survivors and their caregivers (587). These challenges adversely affect treatment and management of cancer and, when not addressed in an effective and timely manner, can lead to long-term morbidity and premature mortality (see **Challenges Faced by Cancer Survivors**, p. 121). 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. 128). Mindfulness—the skill of bringing one's attention to whatever is happening in the present moment in a thoughtful and nonjudgmental manner—is one approach by which psycho-oncology helps alleviate physical distress, while simultaneously focusing on mental well-being (588). Ongoing research is focused on better understanding the impact of these approaches in improving quality of life for cancer survivors (589). Cancer survivors and their caregivers should discuss with health care providers whether psycho-oncology-based interventions will be beneficial to them.

Delivering Care to Cancer Survivors

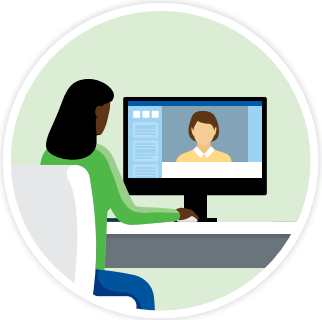
Over the past five decades, the number of cancer survivors has steadily increased, thanks to advances in cancer screening and treatment (see **Figure 25**, p. 121). Furthermore, cancer survivors are living longer and fuller lives. These improvements highlight the need to develop a strong and equitable care system to support long-term survivorship.

COORDINATING CARE

Deteriorated overall health, increased financial burden, and reduced quality of life are only a few of the numerous challenges cancer survivors face compared to healthy individuals. The multifaceted impact of cancer diagnosis and treatment results in complex health care needs. These

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:



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 (591).

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 (592).

Participating in mindfulness-based interventions significantly reduced the severity of anxiety and depression, and improved quality of life, in adults with cancer up to six months after delivery of mindfulness sessions compared to usual care or no intervention (593).

needs can only be met by a comprehensive and coordinated approach that ensures efficient and equitable delivery of care to all cancer survivors.

A well-coordinated care plan has the potential to deliver maximum benefit to patients by decreasing their risk of long-term morbidity and premature mortality and by improving their quality of life. Optimal coordinated care recognizes that cancer is a complex disease which requires multiple appointments with health care providers and rounds of treatments, as well as support and follow-up care in multiple aspects of life from specially trained health care providers (593). Eighty-six percent of participants in a webinar on the needs for a well-developed coordinated care plan emphasized the importance of identifying key outcomes and measures—tailored for the unique and different needs of different cancer survivors—as well as using digital health approaches to implement and assess quality care coordination (594).

Researchers are also investigating how innovative digital health strategies such as telehealth can help cancer survivors relieve adverse effects of their cancer experience. Telehealth, also called telemedicine, is the distribution of health-related services and information using telecommunication technologies, such as the internet and smartphone applications (407). A recent study found that telehealth-based interventions significantly improved quality of life among cancer survivors when compared to usual care (595). The COVID-19 pandemic has further uncovered the potential of telehealth in providing care for cancer survivors. A recent survey found that 95 percent of childhood cancer survivors, whose long-term in-person follow-ups had to be conducted virtually by videoconference during the peaks of the COVID-19 pandemic from April to June 2020, expressed complete or high satisfaction with the experience. Importantly, 66 percent of the survivors considered virtual visits as helpful or nearly as helpful as in-person visits, and 82 percent preferred that these visits remain an option after the pandemic (596).

Frequent communication between cancer patients and their care team is central to making shared health care-related decisions. According to a recent analysis of web-based surveys of clinicians and patients, 98 percent of patients and 70 percent of clinicians found that electronic access to records that included notes from clinic visits and information on diagnosis and treatment was valuable for developing and coordinating an effective care plan (597). Information gleaned from such studies

provides the basis to develop evidence-based approaches to coordinated care that increases the well-being of cancer survivors throughout their experience with cancer.

THE IMPORTANT ROLE OF CAREGIVERS

Caregivers play a central role in any coordinated care team for a cancer survivor from the time of diagnosis through the entire cancer experience. As the number of cancer survivors increases, the number of trained caregivers (for example, health care professionals) as well as informal caregivers (for example, spouses) is also on the rise. Nearly three million Americans care for an individual who has been diagnosed with cancer (598), and the majority are informal caregivers. According to a recent study, more than 55 percent of cancer survivors reported having an informal caregiver during or after their cancer treatment (599).

As the health care needs of cancer survivors range widely depending on many factors such as the age at which a person was diagnosed with cancer and the type of treatment received, both trained and informal caregivers face mental and emotional challenges when taking care of a cancer survivor (600). However, adverse effects of cancer are felt at a deeper level by informal caregivers, who often struggle with the dual burden of providing complex clinical care and managing personal emotional distress (601). The COVID-19 pandemic has further added to the stress associated with caring for cancer survivors. According to one study, 60 to 70 percent of parents who were caring for an AYA with brain tumor during the pandemic reported worsened mood and increased anxiety during this time (602). Researchers are investigating ways to develop approaches that can help cancer caregivers cope with the stress of caring for an individual with cancer. As one example, researchers have found that family caregivers who received emotion regulation therapy, an evidence-based approach to counter distress (603), reported significant reductions in psychological distress and worries (604). Increased focus on and awareness of the unmet needs of cancer caregivers underscore the potential of a well-developed in-home care system—that includes caring for the well-being of caregivers—for improving clinical outcomes and quality of life for cancer survivors.

LOOKING TO THE FUTURE

In this section, you will learn:

- The next generation of technologies that are fueling the full spectrum of cancer science from bench to bedside will accelerate the pace of our understanding of cancer biology while transforming the future of clinical practice.
- Combining genomic and proteomic approaches in cancer research will revolutionize treatment by expanding precise use of existing therapeutics and addressing some of the most elusive questions in cancer such as treatment resistance.
- Artificial intelligence holds enormous promise in cancer science and medicine and may transform the future of cancer detection, diagnosis, treatment, and drug discovery.
- The new wave of innovation in science and technology is providing researchers with the necessary tools to effectively target cancer-driving molecules that have long been "undruggable."
- Implementation science aims to integrate proven, effective interventions into everyday life and routine health care in order to bridge the gap between evidence and clinical practice.

These are unprecedented times for the medical research community. While advances across the spectrum of cancer science and medicine are fueling unparalleled progress against cancer and driving down the U.S. cancer death rates, the medical research community has also faced extraordinary adversity over the past two years in the face of the COVID-19 pandemic. However, many researchers, including **AACR President, 2021–2022, David A. Tuveson, MD, PhD, FAACR**, are extremely hopeful about the future because they are confident that through innovative and collaborative research, we will power more advances against cancer while we continue to control the public health crisis caused by COVID-19 (see p. 136). The new wave of scientific and technological innovations discussed in this chapter has the potential to transform cancer research and patient care in the years to come.

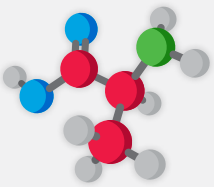
Proteogenomics: A New Frontier in Precision Cancer Medicine

As described in **Understanding How Cancer Develops** (see p. 27), the order of the four bases in DNA provides the code used by a cell to produce the various proteins it needs to function. The genetic code in the DNA is first converted into another molecule called ribonucleic acid (RNA) which is then used by the cell to manufacture proteins. Once manufactured, proteins undergo various chemical modifications such as receiving carbohydrate or lipid tags leading to the formation of a mature protein. All important functions within a cell are carried out by proteins. One can generally conclude that normal DNA encodes normal proteins, which helps produce normal cells, which assemble into healthy tissues. Conversely, altered DNA leads to altered proteins which may lead to unhealthy tissues and tumor development.

While cancer genomics—the comprehensive analysis of tumor-associated genetic changes—has become a core component of modern precision medicine, looking exclusively at the DNA (or RNA) provides an incomplete picture of the biological underpinnings of cancer etiology. This is because mutational analysis, albeit an important tool, cannot always reliably predict changes in the level or function of the corresponding proteins. Such limitations are highlighted by the fact that while genomic databases, such as The Cancer Genome Atlas, catalog numerous genetic changes associated with multiple cancer types, the impact of many of those mutations on cellular function or on patients' outcomes remains unknown. It should also be noted that even though the presence of specific genetic alterations is frequently used as a biomarker to determine whether a patient is eligible for treatment with a molecularly targeted therapeutic, the main component of precision medicine, most of these therapeutics work by binding to tumor proteins. Adding proteomics—the comprehensive analysis of all the proteins inside a cell—to the armamentarium of cancer research, can 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. This

Launched in 2011, the NCI's **Clinical Proteomic Tumor Analysis Consortium (CPTAC)** is a national effort to accelerate the understanding of the molecular underpinnings of cancer through the application of proteogenomics.



- The goal of CPTAC is to advance precision cancer medicine by leveraging proteogenomics.
- In 2016, CPTAC created two additional programs to further accelerate proteogenomics research.
  - **The Applied Proteogenomics OrganizationaL Learning and Outcomes (APOLLO)** network partners with the Department of Defense and Veterans Administration to identify ways to make proteogenomic analyses part of a patient's routine cancer care.
  - **The International Cancer Proteogenome Consortium (ICPC)** facilitates collaboration of more than 10 countries to study common cancers with the goal of enhancing precision oncology and global data sharing.
- All research resources and data generated are made available to the public.

includes understanding when proteins get made and what modifications occur to proteins after they are made that may switch them on or off. Ongoing research on cancer proteogenomics, much of which is led by the NCI's Clinical Proteomic Tumor Analysis Consortium (CPTAC), is aimed at uncovering novel insights into the cellular and molecular basis of cancer development and identifying potential new therapeutic interventions that cannot be obtained through genomics alone (605–610).

Using proteogenomics, researchers can classify tumors based on their molecular characteristics rather than cellular morphologies, which has traditionally been the leading approach for tumor classification. Identification of the molecular characteristics provides key insights to a tumor's potential therapeutic vulnerabilities. As one example, a comprehensive proteogenomic analysis of more than 100 breast cancer samples performed in a recent study provided an in-depth look at the inappropriate activation of certain cellular pathways and aberrant cellular metabolism within subsets of breast cancers. The researchers identified a subset of patients with hormone receptor-positive breast tumors, who are usually treated with targeted therapeutics, as potential candidates for treatment with immune checkpoint inhibitors, thereby increasing the utility of these revolutionary immunotherapeutics in a new group of cancer patients (607). In a second study, proteogenomic analysis helped researchers understand why certain patients diagnosed with head and neck cancers whose tumors present abnormal levels of EGFR or the immune checkpoint protein PD-L1 still do not respond to EGFR-targeted therapeutics or immune checkpoint inhibitors (609). These data are critical for the selection of appropriate patient populations that are most likely to respond to EGFR-targeted therapies or immunotherapies. In addition, the study identified novel targets that could be used for the development of future checkpoint inhibitors against these aggressive cancers. Yet another recent proteogenomic analysis from more than 200 pediatric brain tumor patients representing seven cancer types offered novel insights into the molecular alterations within brain tumors and revealed previously unknown therapeutic avenues for certain children with brain cancers (608). The data uncovered a new molecularly targeted treatment option for certain children with a brain tumor known as craniopharyngioma, which currently has no effective therapeutic options.

Novel insights obtained through proteogenomic analysis of cancers have tremendous diagnostic and therapeutic potential and may provide answers to some of cancer's most elusive questions such as treatment resistance and recurrence. However, the use of proteogenomics is not yet a part of routine clinical practice. Some of the current challenges that researchers are trying to overcome include identifying methodologies that allow for combined analysis of DNA, RNA, and protein from limited tissue samples obtained through biopsies (611); improving tissue acquisition techniques; and overcoming logistic and workflow barriers to maintain accurate documentation of samples in large-scale research studies (612). Going forward, we anticipate that the next wave of innovation in science and technology along with advances in cross-disciplinary collaboration, data sharing, and patient engagement will lead to the integration of proteogenomics into the fabric of cancer research and care. This exciting new frontier in precision cancer medicine is poised to transform the future landscape of cancer diagnosis, prognosis, and treatment, bringing new hope to many more patients with cancer.

Artificial Intelligence: Shaping the Future of Cancer Science and Medicine

According to NCI, artificial intelligence (AI) is defined as the ability of a computer to perform functions that are usually thought of as intelligent human behavior, such as

learning, reasoning, problem solving, and decision-making. As researchers accumulate large quantities of cancer-related data ranging from tumor images from scans or pathological slides, to tumor sequencing, electronic health records, and clinical outcomes, AI can analyze this information to derive meaningful insights that previously could not have been realized (613). Machine learning is an application of AI that focuses on the development of computer programs that can access and learn from data, identify patterns, and make decisions without explicit human intervention. Deep learning is a subset of machine learning that utilizes neural networks to make decisions. The applications of AI in cancer science and medicine are vast and rapidly expanding. For instance, AI has the potential to streamline processes for radiological and pathological image interpretation allowing for faster decision-making for people with life-threatening cancers. Several clinical applications of AI in radiology and pathology were discussed in *AACR Cancer Progress Report 2020* (467). Some recent advances in the field that are already benefiting patients are described in previous chapters in this report (see **Enhancing the Speed and Accuracy of Interpreting Screening Tests**, p. 60, and **Using Artificial Intelligence for Precision in Surgical Oncology**, p. 82). In this section we provide a brief overview of selected exciting new AI approaches that are currently in investigation and may provide future breakthroughs in cancer care.

TRANSFORMING DRUG DEVELOPMENT

Researchers are harnessing the power of AI in different ways to accelerate drug discovery for many diseases including cancer (614–616). Some efforts are aimed at accelerating the pace of basic research such as identifying new targets, while others are designed to make clinical trials more efficient. The use of AI can potentially improve each step of the drug development process (see sidebar on **Therapeutic Development**, p. 74). For instance, AI can harness massive amounts of information from the scientific literature, clinical databases, and patient-derived data to identify potential new drug targets, such as proteins that are vital for cancer growth; to design new therapeutics that target such proteins; and to help evaluate the safety and effectiveness of those therapeutics (617).

As mentioned in the discussion of proteogenomics, most molecularly targeted therapeutics that are an integral part of precision medicine target tumor-associated proteins in cancer cells or in the tumor microenvironment. To design therapeutics that can effectively attach to and modulate protein function, researchers must know the 3-dimensional structure of proteins. Traditionally, solving protein 3-dimensional structures has been difficult and time-consuming since it requires complex experiments, including crystallization of proteins followed by visualization using X-rays and highly sophisticated electron microscopes. Recently, an AI program called AlphaFold was shown to be able to predict 3-dimensional structures of proteins with incredible precision and accuracy (354,618,619). In fact, the program outperformed around 100 research teams in a prestigious biennial protein-structure prediction challenge called Critical Assessment of Structure Prediction. Researchers have further used AlphaFold to predict the structures of almost all 20,000 proteins that are expressed by the human genome as well as many others belonging to other organisms (620). Scientists anticipate that tools such as AlphaFold will help drug development researchers predict the 3-dimensional structures of proteins of interest rapidly and economically. They are confident that AlphaFold as well as other similar AI platforms will revolutionize the future of drug development for complex diseases such as cancer by significantly decreasing the time and costs associated with traditional approaches (620,621).

Decades of basic research have taught us that immune cells called T cells are naturally capable of destroying cancer cells. We have also learned that tumors evade destruction by T cells because they have high levels of proteins that attach to and trigger "brakes" on T cells, stopping the T cells from attacking the tumor (see **Releasing the Brakes on the Immune System**, p. 107). These brakes, which are proteins on the surface of T cells, are called immune checkpoint proteins. It took researchers over a decade since the discovery of the first checkpoint inhibitor to develop therapeutics that target these proteins. Checkpoint inhibitors have revolutionized cancer treatment, even for patients with very advanced cancers. Notably, the impact of AI in accelerating immune checkpoint drug development is evident from recent research. As one example, an AI platform was able to discover a potential checkpoint inhibitor candidate within only eight months (622). The therapeutic blocks the activation of the checkpoint protein adenosine 2a receptor on T cells, for which there are no currently available inhibitors approved by FDA. Based on promising preclinical data from pancreatic and lung cancer models which show that the therapeutic is able to activate cancer-fighting T cells and reduce the number of viable tumor cells (623), the candidate molecule will soon be evaluated in phase I clinical trials (624).

One of the most pressing challenges in drug development is low patient participation in clinical trials, especially for racial and ethnic minorities and other underserved populations (see sidebar on **Disparities in Cancer Clinical Trial Participation**, p. 79). Overcoming barriers to clinical trial participation is a major focus for all stakeholders in the cancer research community. Data from recent studies indicate that AI platforms can play a critical role in these efforts. A known barrier for minority patients' participation in clinical trials is restrictive and sometimes poorly justified eligibility criteria for patient inclusion. A new report, which used an AI platform to harness data from electronic health records from more than 60,000 lung cancer patients and publicly available trial eligibility criteria from clinicaltrials.gov to evaluate the real-world impact of eligibility criteria on patient recruitment and outcomes, found that many patients who were excluded from certain trials due to the restrictive criteria could have benefited from treatments

provided in the trials (625). In fact, when the researchers broadened the eligibility criteria using the AI-guided approach, the estimated number of eligible patients more than doubled. Notably, the study also found that trials with broader eligibility did not have any more adverse event-related treatment withdrawals compared to trials with strict eligibility criteria. AI-driven methodologies such as the one used in this study can be critical in the future design of more inclusive clinical trials while still maintaining patient safety.

PREDICTING PATIENT OUTCOMES

Across the continuum of cancer care, there is growing interest in utilizing AI to harness patients' data to guide disease management such as evaluating cancer susceptibility for high-risk individuals, making treatment decisions, and predicting treatment responses and long-term outcomes (626–629).

Patients with HCV infection-induced chronic cirrhosis have a high risk of developing a form of liver cancer known as hepatocellular carcinoma. According to a recent retrospective analysis, an AI program outperformed standard statistical models at identifying individuals with liver cirrhosis who were likely to develop liver cancer (628). By predicting which individuals had the highest risk of developing cancer the AI program provides avenues for prioritizing patient surveillance and treatment. In a second study, a deep learning-based AI approach was able to use CT images from patients with stage IV NSCLC that contained alterations in the EGFR gene to identify which patients are most likely to benefit from EGFR-targeted therapeutics (627). These data can help health care providers not only to select patients who are most likely to benefit from therapy, but also to spare those who are unlikely to benefit to avoid unnecessary adverse effects of such treatments. In a third study, a machine learning program was able to utilize data from electronic health records to prospectively identify cancer patients who are at high risk of short-term mortality within six months after their encounter with the health care system (626). Such AI-based tools may allow health care providers to inform appropriate behavioral interventions for patients and engage in a timelier conversation regarding the patients' goals of care and end-of-life preferences.

Collectively, these studies emphasize the incredible potential of AI for the future of clinical cancer care. However, one area where researchers must pay close attention is the inclusion of datasets from diverse populations that are representative of the overall U.S. cancer patient population during the development of AI platforms. Lack of diversity in the data that are used to develop AI or machine learning systems may incorporate racial/ethnic or other biases within AI applications and limit their generalizability for different patient population groups who must benefit from these state-of-the-art technologies. As one example, since many of the AI programs aimed to detect skin cancers were trained primarily on light-skinned individuals, there are concerns that these tools perform poorly in detecting skin cancer affecting individuals with darker skin (630). Similar concerns have been raised by experts in cancer genomics research based on many recent findings demonstrating that samples used in cancer genomics research projects such as cancer-related genome-wide association studies are collected primarily from white populations (631). Addressing these challenges will require both short- and long-term approaches ranging from more diverse data collection and AI program monitoring to infrastructural changes such as diversification of the funders and developers of AI research, publication, and education (632).

New Wave of Innovation to Aim at Cancer's Most Intractable Targets

Since the signing of the National Cancer Act 50 years ago, there has been unprecedented progress in the treatment of the collection of diseases we call cancer. The newest pillars of cancer treatment, molecularly targeted therapy and immunotherapy, which form the foundation of precision medicine, have revolutionized care for many patients leading to remarkable durable responses even in individuals with metastatic cancer. Notably, a majority of these cutting-edge cancer treatments are small molecules or antibodies which work by physically binding to cellular proteins in tumors and blocking their function. Unfortunately, targeted therapeutics and immunotherapeutics are only available for a selected number of patients with certain types of cancers and even among patients with cancers that are targetable with molecularly targeted therapeutics or immunotherapeutics, most patients ultimately develop resistance to these drugs.

Even though numerous genes and their encoded proteins have been shown to be altered in cancers, one of the key challenges in precision medicine is that scientists, so far, have only been able to successfully target a fraction of these molecules therapeutically. For instance, while it has been long recognized that mutations in TP53, RAS, or MYC genes can promote tumor growth and are very common in many cancers, the respective proteins have been difficult to target.

THE HONORABLE
Brenda Lawrence

U.S. Representative for Michigan's 14th District

"In celebration of the 50th anniversary of the National Cancer Act, we recognize how far we've come and renew our commitment to bold action to fight cancer. I'll continue to support federal investments in cancer research and the invaluable, lifesaving work of AACR."

THE HONORABLE
Bill Cassidy

U.S. Senator for Louisiana

"Thanks to major breakthroughs in research and treatment, there is hope to prevent, detect, and cure cancer. We have made tremendous progress in the 50 years since the passage of the National Cancer Act, but still have a ways to go. Federal investment and innovative research will continue to pave the way in the fight against cancer."

The key challenges that have prevented researchers from developing therapeutics against some of these proteins include their location within a cell and their structure. Proteins localized on the surface of a cell are easier to target compared to those that are inside a cell. In addition, it is easier for scientists to design therapeutics against proteins that have ordered 3-dimensional structures and defined binding pockets which can serve as efficient docking sites for the therapeutics. Often these binding pockets are adjacent to the active sites, which are regions of the protein that are critical for their function. In fact, many proteins that have been difficult to target, e.g., p53, RAS, or MYC, are localized inside the cell and possess highly disordered and labile 3-dimensional structures. Powered by a new wave of scientific and technological innovations, such as those described here, researchers are now looking into exciting new approaches to target some of the most intractable proteins involved in cancer development.

FLAGGING CANCER CELLS FOR DESTRUCTION BY THE IMMUNE SYSTEM

Immunotherapeutics unleash a patient's own immune system to fight cancer and can work in different ways. One approach that researchers have utilized for the development of immunotherapeutics is designing molecules that flag cancer cells in some way for detection and destruction by the immune system (see **Unleashing the Body's Defense System Against Cancer**, p 117). Antibodies are a class of immune system proteins that are frequently used to flag cancer cells. In two recent studies, researchers were able to target two of the most elusive proteins associated with cancer, RAS and p53 (633,634), using engineered antibodies. Mutations in RAS and p53 have been detected in 50 percent and 30 percent of all tumors, respectively, and although there has been some recent progress in treating cancers driven by RAS mutations (see **A New Breakthrough in Treating Lung Cancer**, p. 91), researchers are still looking for ways to target p53. Targeting p53 mutations has been particularly challenging since in many cases the mutant form of the protein is inactive, and since most cancer drugs work by blocking the function of overactive proteins rather than restoring the function of inactive ones. In addition, both RAS and p53 are located inside the cell making therapeutic targeting of these molecules especially difficult.

Decades of basic research in cancer immunology, coupled with the latest advances in molecular biology, proteomics, and bioinformatics tools, have enabled researchers to overcome some of the challenges in drug targeting. It is now known that cells display fragments of intracellular proteins on their surface during a process that is needed for normal immune function. In the case of cancer cells, some of these fragments are parts of mutated proteins which are specific only to cancer cells but absent in normal healthy tissue. By using this knowledge, researchers were able to design bispecific antibodies that attached to fragments of either mutated p53 or RAS on the cancer cell surface with one end and to immune cells with the other end. By bringing immune cells close to cancer cells the antibodies help immune cells to recognize and eliminate cancer cells. In preclinical studies, these antibodies were able to slow tumor growth. These data highlight an exciting new approach in targeting difficult to reach proteins, and future research will determine whether these novel antibodies can improve outcomes for patients with cancer harboring mutations in p53 or RAS.

MOBILIZING TARGETED PROTEIN DEGRADATION

The proteasome is a molecular machine naturally found in cells that breaks down proteins the cell no longer needs. The process helps control multiple functions including cell division and survival. Selective degradation of cancer-causing proteins using the proteasome machinery is an approach that is currently being tested, especially for proteins that have been difficult to target by conventional methods (635). One area of active investigation is the development of Proteolysis Targeting Chimeras (PROTACs), a class of therapeutics that can induce targeted degradation of disease-causing proteins (635–637). These bifunctional small molecules consist of two protein-binding elements that are attached by a linker; one binds to the protein of interest (target) and another recruits an E3 ubiquitin ligase, a key component of the proteasomal machinery. By bringing the target close to the E3 ligase, PROTACs initiate breakdown and elimination of the target proteins.

Because of their unique mechanism of action, PROTACs have certain advantages over traditional cancer treatment using small molecule inhibitors or antibodies (e.g., most molecularly targeted therapeutics or immunotherapeutics) which work by physically binding to cellular proteins in tumors and blocking their function. An ongoing challenge in treatment with molecularly targeted therapeutics or immunotherapeutics is the development of treatment resistance (see sidebar on **Treatment Resistance**, p. 93). Common mechanisms by which cancer cells become resistant to therapeutics are by increasing the levels of target proteins or by gaining new

mutations in the target proteins. Since PROTACs work by destroying rather than inhibiting target proteins, treatment with PROTACs can overcome these pathways of treatment resistance. Another advantage with this type of therapeutics approach is that PROTACs are recycled after they degrade their target proteins. Therefore, one molecule of PROTAC can eradicate multiple copies of the target protein. Thus, a smaller dose of PROTACs compared to small molecule inhibitors might be as effective in producing a desired antitumor effect. Furthermore, since PROTACs do not need to bind to the active sites of target proteins, they can be easier to design against otherwise intractable targets.

PROTACs targeting a wide range of targets for many cancer types are currently in different phases of preclinical and clinical development (638). Among these are efforts to use PROTACs to degrade otherwise difficult to target cancer-causing proteins such as p53, STAT3, RAS, MYC, etc. (638–641). To maximize their therapeutic function, researchers are exploring ways to activate PROTACs in tumor-specific manners as well as in selected tissues. In this regard, there are ongoing efforts aimed at developing modified versions of PROTACs such as those that can be activated by irradiation or attachment to tumor-specific ligands (e.g., Antibody Conjugated Bifunctional Degraders) (635). Targeted protein degradation using PROTACs, as well as the newer generation of more sophisticated protein degraders, holds great promise for the future of cancer medicine and may transform cancer treatment by overcoming some of the most challenging obstacles in current precision medicine.

Accelerating Cancer Control Efforts Through Implementation Science

Research discoveries are the driving force behind every clinical intervention that improves survival and quality of life and every new policy designed to advance public health. However, there is a gap between what we know can improve public health and what gets implemented in everyday life and in clinical practice. This gap creates a substantial impediment to public health. According to NCI, implementation science is a field of research that utilizes scientific approaches to find the best ways to integrate proven, effective interventions into routine health care and public health settings to bridge the gap between evidence and practice. Implementation science is fundamental to cancer control, which is defined as a collective approach aimed at reducing cancer risk, incidence, morbidity, and mortality, and improving quality of life.

As discussed earlier in the report, there is substantial evidence that HPV vaccination among adolescents can prevent HPV-related cancers and that cancer screening among average-risk individuals can reduce mortality from the screened cancer. However, in the United States, the current uptake of HPV vaccination as well as cancer screening tests is suboptimal among the eligible populations (see sidebar on **Suboptimal Use of Cancer Screening Tests**, p. 69). Similarly, there are limitations in the uptake of genetic testing of tumors in clinical practice, even though this is an area with proven health benefits for cancer patients (642). Closing the gap between our current knowledge of cancer etiology, prevention, diagnosis, treatment, and survivorship and what is provided as standard care will require significant advances in implementation science. Beyond the United States, implementation science will be key to efforts aimed at reducing the global burden of cancer because it can accelerate cancer control, especially in low- and medium-income countries (LMICs) which are disproportionately affected by cancer.

Researchers are currently assessing implementation of numerous cancer interventions across the continuum of clinical care. Areas of high priority include local adaptation of broad evidence-based interventions, long-term sustenance of effective interventions, advancement of cancer health equity, and policy implementation, as well as de-implementation of harmful or suboptimal practices (e.g., cancer screening among those who may not benefit from screening, such as individuals above the recommended screening age) (643). Ongoing investigations in implementation research, many of which are funded by NCI, focus on diverse topics that include increasing cancer screening in underserved communities, enacting tobacco control policies, and improving care of cancer survivors, among others (644). The overarching goal of these projects is to develop interventions that improve cancer outcomes in both clinical and community settings. To maximize the impact of implementation research on public health, NCI is pursuing a multipronged approach that includes developing methodologies and measures to advance implementation science, increasing access to tools and resources for implementation research (e.g., establishing implementation science laboratories in both health and community settings), disseminating knowledge and data on evidence-based cancer control interventions to all stakeholders, and establishing training programs such as Mentored Training in Dissemination and Implementation in Cancer.

Implementation science was recognized as one of the scientific priority areas by the Cancer Moonshot Blue Ribbon Panel. In September 2019, NCI launched the Implementation Science Centers in Cancer Control initiative to advance this priority. The Blue Ribbon Panel had identified several areas of focused support including: accelerating the delivery of colorectal cancer screening, follow-up, and referrals to care in regions of the United States where screening rates are below national standards; enhancing the delivery of tobacco cessation treatments; and developing approaches to identify and care for individuals with inherited cancer syndromes (645).

The field of implementation science is ripe with opportunities and holds immense potential for reducing the burden of cancer for all Americans (646). It is hoped that, through coordinated efforts across national, regional, local, and community partners, implementation science can translate knowledge generated from research discoveries into clinical practice and transform the delivery of evidence-based care across the cancer control continuum.

Envisioning Future Progress Against Cancer Driven by Advances Across the Continuum of Cancer Science and Medicine

David A. Tuveson, MD, PhD, FAACR AACR PRESIDENT, 2021–2022
Director and Roy J. Zuckerberg Professor of Cancer Research
Cold Spring Harbor Laboratory Cancer Center, Cold Spring Harbor, New York

Over the course of my career as a physician-scientist, the field of oncology has undergone a remarkable transformation. With the application of science and technology, the reality for a cancer patient has changed dramatically. Now, almost every patient with cancer has a real hope of getting healthier. I anticipate that the next wave of innovations will get us to the point where we not only provide hope but help all patients so that they can return to "life as they knew it" before their diagnosis.

When I was in medical training, most patients with cancer were treated with surgery, radiotherapy, and/or chemotherapy. These treatments helped some, but most patients with metastatic cancer did not have curative options. The landscape of cancer care has changed drastically over the past three decades through the knowledge generated by scientific and technological innovations. For instance, sequencing of the human genome led to the revolution of molecularly targeted therapeutics, which has transformed treatment for many patients. As one example, basic and clinical research starting from the identification of the KRAS gene all the way to the recent FDA approval of the KRAS-targeted therapeutic sotorasib for certain patients with lung cancer highlights how research-driven advances can improve patient outcomes. Another great example is the development of immunotherapeutics, which was propelled by basic research in immunology, and has now become a standard treatment for many adult and pediatric patients with formerly lethal cancers. Because of these exciting advances, oncology is one of the most promising areas of medical research where current trainees can truly help people from disease back to health. Of course, there is a substantial amount of work that is left to be done.

As we look to the future, the new wave of scientific and technological innovations will accelerate progress in cancer prevention, detection, diagnosis, and treatment. A greater understanding of the tumor microenvironment and ways to modify it will help us develop better strategies to treat cancers. Identifying more sophisticated approaches to delivering cytotoxic agents such as radioactive compounds specifically to tumors will enhance our ability to eliminate cancer cells. An emerging class of therapeutics that holds immense potential is protein degraders called PROTACs that can selectively destroy cancer-causing proteins.

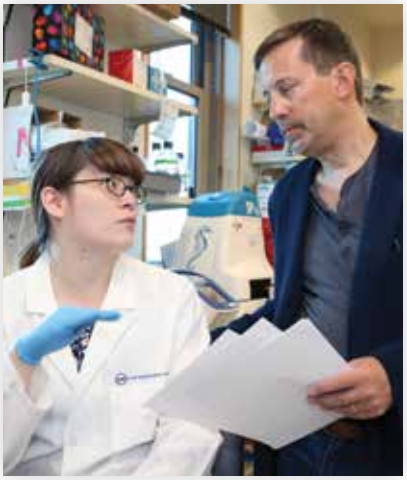
We must also fundamentally change how clinical research is conducted. Currently, only five percent of adult cancer patients participate in clinical trials and participation is especially low among racial and ethnic minorities. We need a cultural change so that in the future every patient is offered and has access to a clinical trial. That is the only way by which we can reach the true potential of precision medicine and answer some of our most elusive questions such as the causes of cancer treatment resistance. It would be critical also to integrate very early-phase (Phase 0) clinical studies prior to large-scale traditional clinical trials where low doses of potential therapeutics are administered to patients to determine whether such treatments may have the desired effect. These data could really help cancer scientists personalize treatments for patients and drive progress in precision cancer medicine.

In parallel to the investigations into cancer biology, there must be a strong focus on studying the "macroenvironment" where an individual lives, the individual's lifestyle and behavior. For instance, we now realize that obesity is a major risk factor for many cancer types; while several hypotheses have been proposed, such as the role of chronic inflammation, the gut microbiome, or hormonal imbalance, the exact mechanism by which obesity leads to cancer is not well understood. Concerted efforts are needed to improve public health measures that can reduce cancer risks especially among segments of the population that experience a disproportionate burden of cancer.

Over the past year and a half, the cancer research community, like every other community around the world, has had to face the COVID-19 [Coronavirus Disease 2019] pandemic, a challenge unlike any that we have faced before. Cancer screening and treatment have been disrupted, most cancer research projects have been halted at least temporarily, and many cancer researchers have turned their attention to fighting COVID-19. However,

the pandemic has also uncovered new opportunities, such as the potential of mRNA vaccines and telemedicine that can have long-term positive impacts on clinical research and delivery of care.

Our past investment in medical research has led to modern medicine, leading to better outcomes for many diseases including cancer. It is vital that we fund meritorious research to encourage the next generation of scientists to get involved in cancer research. This will require sustainable funding at the National Cancer Institute that is higher than the current rate. It is imperative that we work together with all stakeholders, including Congress, so that medical research continues to be a national priority. Increased federal investment is urgently needed for us to fulfill our mission of preventing and curing all types of cancers and bring more hope to our patients.



COMBATING CANCER THROUGH SCIENCE-BASED, PATIENT-CENTERED POLICIES

In this section, you will learn:

- Federal funding for medical research, specifically through NIH and NCI, has a significant impact on our nation's health and the United States economy.
- Regulatory science initiatives at FDA are vital to accelerating progress against cancer and require robust federal funding to support the development of safe and effective therapies.
- Policies and federally funded public health programs, many of which are supported by CDC, ensure that individuals have access to preventive services, screening, and coverage for cancer treatment.
- Tobacco control policies improve public health and reduce cancer risk.
- Newly passed legislation aims to improve outcomes for children and adolescents who are diagnosed with cancer.
- Patient advocates play a vital role in educating patients with cancer, serving on many of the advisory boards and committees related to cancer research, and raising funds for cancer research.

The mission of NIH is to seek fundamental knowledge about the nature and behavior of living systems and to apply that knowledge to enhance health, lengthen life, and reduce illness and disability. A key goal of the agency is to develop, maintain, and renew scientific human and physical resources to ensure a continued high return on the public investment in research. NIH leadership and peer-review processes exemplify and promote the highest level of scientific integrity, public accountability, and social responsibility in the conduct of biomedical research. In realizing these goals, NIH improves the health of the nation by conducting and supporting research to address the greatest health challenges facing our society (647).

NCI, under the NIH umbrella, leads, conducts, and supports research across the nation to advance scientific knowledge and drive progress against cancer, a collection of more than 200 devastating diseases that impact nearly every family.

The collective progress made against cancer during the 12 months covered in this report was built on decades of publicly funded science through NIH and NCI. Robust and sustained funding for medical research is critical to continuing this progress, as discussed by **Congresswoman Jaime Herrera Beutler** (see p. 142). From fiscal year (FY) 2015 to FY 2021, Congress has worked in a bipartisan fashion to increase the overall NIH appropriations by nearly $13 billion or 42 percent (see **Figure 26**, p. 139). This remarkable investment is fueling the next wave of discoveries, thanks in large part to the leadership of Chair Rosa DeLauro (D-CT), Ranking Member Tom Cole (R-OK), Chair Patty Murray (D-WA), and Ranking Member Roy Blunt (R-MO) in their respective roles on the Labor-HHS-Education Appropriations Subcommittees in the House and Senate.

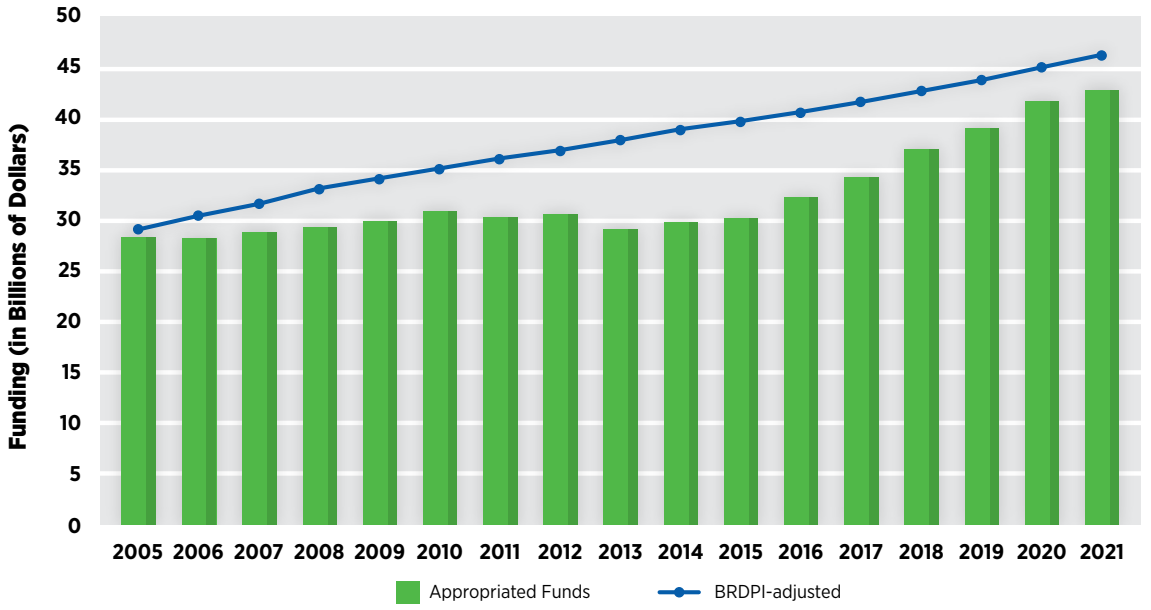
The mission of the Oncology Center of Excellence (OCE) at FDA is to achieve patient-centered regulatory decision-making through innovation and collaboration. The agency plays a critical role in reviewing new breakthrough treatments to ensure that they are safe and effective for patients with cancer.

CDC is another equally important federal partner in fueling progress against cancer, as it brings science-driven public health interventions, including cancer screening and prevention programs, to communities across the country. CDC's Division of Cancer Prevention and Control 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.

The COVID-19 pandemic has had a profoundly negative impact on cancer research and care. For months, many research laboratories were closed or had to significantly alter their operations, while hundreds of promising clinical trials were put on hold and dozens permanently terminated (648,649). Resources were shifted to respond to the immediate threat of the pandemic, and many researchers lent their expertise and supplies to addressing the public health emergency. While most research operations have returned to some level of normalcy, the impact of these disruptions will be felt for years. NIH

FIGURE 26

NIH FUNDING



Congressional appropriations leaders have worked in a bipartisan way to increase NIH funding by nearly 42% from fiscal year (FY) 2015 to FY 2021. The biomedical research and development pricing index (BRDPI) is a measure of the rising cost to conduct medical research. The significant funding increases provided by Congress in recent years have narrowed the gap between BRDPI and appropriated funds following years of essentially level funding.

Director Francis Collins, MD, PhD, has estimated that more than $16 billion worth of biomedical research productivity has been lost since the pandemic began (650). The consequences have been especially severe for early-career researchers, women, and underrepresented minorities (651–653).

Robust annual funding increases will be essential for NIH, NCI, FDA, CDC, and other agencies to continue their vital work against cancer. Supplemental research funding for NIH will also be necessary to respond to the losses incurred by the medical research enterprise because of the pandemic. Meanwhile, new legislation, as well as policies and programs carried out by federal agencies, will play a key role in furthering our progress against cancer.

THE HONORABLE
Fred Upton

U.S. Representative for Michigan's 6th District

Vice Chairman, Senate Appropriations Committee

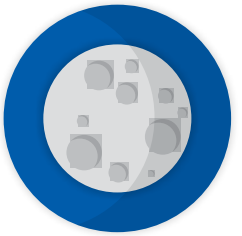
"I'm "all in" for this cause. This has always been an important crusade and as I serve on the Energy and Commerce Committee I will continue to lead the bipartisan effort to do more!"

Investing in a Healthier Future Through Research

The 27 Institutes and Centers that comprise NIH represent the core of the U.S. biomedical research infrastructure by providing the majority of annual research grant and contract opportunities. NIH- and NCI-funded research grants and contracts have led to new discoveries across the broad field of cancer science, laying the groundwork for innovative new

THE NATIONAL CANCER MOONSHOT INITIATIVE

Congress passed the 21st Century Cures Act in December 2016, authorizing $1.8 billion in funding for the Cancer Moonshot over seven years. Less than five years after the Cancer Moonshot was launched, we have made remarkable progress and realized valuable scientific accomplishments.



To date, NCI has invested over $1 billion in Moonshot funding, which is supporting greater than 240 research projects across more than 70 cancer science initiatives. This investment has led to many important insights tied to the Moonshot's key research priorities set forth by the Blue-Ribbon Panel (BRP) Report. Across these initiatives are the cross-cutting themes of reducing cancer health disparities, increasing data sharing, and creating synergistic collaborations and partnerships. With specific Moonshot funding set to end after fiscal year 2023 NCI is in the process of determining opportunities to maintain the important infrastructure built through, and to continue momentum in, Moonshot activities. In addition, NCI continues to maintain support for its broad research portfolio of investigator-initiated research, cancer centers, clinical trials, and workforce training.

By focusing on areas of cancer research that are most likely to benefit patients as a result of new investment, the Cancer Moonshot has brought together a large community of investigators and clinicians who are dedicated to expediting research to improve the lives of people with cancer and their loved ones. Below are a few featured projects that highlight some of the progress that has been made to date:

Creation of the Fusion Oncoproteins in Childhood Cancers (FusOnC2) Consortium to determine mechanisms of childhood cancers. This includes developing a test that can help identify drugs that may degrade the EWS/FLI1 protein—the key cancer-promoting protein in most Ewing sarcoma tumors.

Integrating novel imaging technologies with molecular analyses to generate 3D human tumor atlases from several types of cancer and making the data available to the community to accelerate the biological understand of cancer and enable predictive modeling for treatments.

Establishing partnerships with 9 advocacy groups and creating a consortium of 33 clinical sites across the country that provide patients access to new clinical trials for rare central nervous system tumors.

Supporting programs focused on ensuring routine delivery of evidence-based tobacco cessation treatment services at more than 50 NCI-designated Cancer Centers.

Expanding the Cancer Research Data Commons, providing data sharing and storage capabilities in the cloud, and supporting the harmonization of cancer research data for the cancer research community to further enable data sharing.

Developing and testing implementation strategies to increase colorectal cancer screening, follow-up, and referral-to-care among underserved populations for whom screening rates are below national standards.

Improving the understanding and development of immunotherapies, including engineering more effective CAR T-cell and other cellular therapies, and identifying potential targets for cancer vaccines.

Utilizing direct participant engagement approaches to boost engagement by American Indians of southwestern tribal nations in cancer genome sequencing programs—with the aim to ultimately enhance cancer prevention and treatment in tribal communities.

For more information and updates, visit **cancer.gov/moonshot**, which includes funding opportunities, a recent seminar series, and a page dedicated to progress.

THE HONORABLE

Anna Eshoo

U.S. Representative for California's 18th District

Chair, House Energy and Commerce Subcommittee on Health

"Cancer is a deeply personal issue for nearly every American. I understand all too well the heartbreak cancer causes and the urgent need to find breakthrough cures. With this year being the 50th anniversary of the National Cancer Act, it's time to seize this moment to invest in the medical research and innovation needed to detect and cure cancer. We must give hope to people who face the death sentences of these diseases today."

therapies, screening and diagnostic tools, and prevention modalities described in this report.

In addition to its extraordinary support for NIH and NCI, Congress has continued to appropriate full funding for the Cancer Moonshot (see sidebar on **The National Cancer Moonshot Initiative**, p. 140), 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. The 21st Century Cures Act, which was signed into law in December 2016, authorized $1.8 billion to fund the Cancer Moonshot over a 7-year period.

Despite the bipartisan congressional support for medical research, NCI is facing significant funding challenges to support investigators seeking research grants and contracts. Remarkable advances in cancer research have stimulated an unprecedented 50 percent increase in the number of research project grant (RPG) applications to NCI since FY 2013. NCI funding, however, has not increased at the same pace, resulting in low payline and declining success rates for investigator-initiated RPGs (654). As a result, NCI is currently only able to fund approximately one of every eight proposals submitted, thus leaving a significant amount of potentially lifesaving cancer science and medicine unexplored. Notably, the 12.8 percent success rate at NCI is significantly lower than the nearly 21 percent NIH-wide success rate for RPGs (655). Furthermore, a fundamental challenge is that women and minority scientists are underrepresented in the biomedical research workforce and are funded at a lower rate (656–661).

Discrepancies in funding will have far-reaching consequences for the cancer research community and the ability to recruit, train, and retain the next generation of cancer scientists. If the success rate for NCI-funded RPGs continues at the current low level, young scientists will be discouraged from choosing careers in cancer research and will likely seek opportunities in other fields. These trends can result in fewer women and underrepresented minorities choosing careers in cancer research. Consequently, the United States may lose its position as the global leader in cancer research.

Congressional leaders have acted to address this issue in both FY 2020 and FY 2021 by providing increases for NCI and specifically including funds to increase the number of research grants funded each year. As a result, NCI raised the payline for R01 grants from eight percent in FY 2019 to 11 percent in FY 2021. Additionally, NCI Director Norman E. Sharpless, MD, asked for $7.6 billion for NCI in FY 2022 as part of his professional judgment budget request. This level of funding would allow NCI to raise its payline for RPGs to the 12th percentile and would set the institute on track to achieving a 15th percentile payline by FY 2025 (654).

Sustaining the U.S. Economy

More than 80 percent of the funds appropriated to NIH by Congress are awarded to scientists in all 50 states and the District of Columbia through a competitive review process. Investments in NIH and NCI also extend well beyond the laboratory and the clinic. As the single largest public funder of medical research in the world, NIH-funded research supported over 536,000 jobs in communities across the U.S. and generated more than $91 billion in economic activity in FY 2020 (662).

The bipartisan commitment to providing steady funding increases for medical research benefits all Americans through new discoveries, while also boosting local economies and creating jobs. With all of the opportunities before us to make advances against cancer, it is vitally important to maintain the momentum. Therefore, policy makers must continue to prioritize robust, sustained, and predictable increases for medical research funding.

Supporting a Vibrant and Diverse Cancer Research Workforce

Continued progress against cancer requires investment in recruiting, training, and supporting the next generation of cancer researchers at every stage of their careers. Within the workforce, early-career researchers are key to ensuring a strong pipeline, bringing in fresh ideas, and addressing innovative questions in cancer research. To realize the full potential of our medical research enterprise, we must also proactively recruit and support a cancer research workforce that reflects the diversity of our society, including diversity in race, ethnicity, gender, and geography. NIH and NCI play an important role in supporting young researchers who will become the scientific and clinical leaders of the future.

Continued on page 144 ▸

U.S. REPRESENTATIVE FOR WASHINGTON'S 3RD DISTRICT | AGE 42

The Honorable Jaime Herrera Beutler

There has not been a person who hasn't been directly or indirectly affected by cancer. For me, cancer took the life of my grandmother. She battled breast cancer successfully once, but then it came back, and ultimately, she lost the battle. My grandmother's experience with cancer, along with the stories of countless others, has shaped my approach to health policy.

As a member of the House Appropriations Subcommittee that determines funding for the National Institutes of Health (NIH) and the National Cancer Institute (NCI), I've worked to increase funding for critical research for the prevention and treatment of various types of cancer. This includes a $488 million increase this year for the NCI, which is vital to advancing cancer research. Another important area is increased access to molecular diagnostic testing – an essential step in choosing the correct treatment for an individual with cancer. In addition to ensuring robust funding for the NIH, it is important to provide substantial resources for the cancer prevention efforts within the Centers for Disease Control and Prevention. Our goal should be to prevent someone from getting cancer in the first place, or at the very least that every community has access to early detection resources.

In addition to putting robust funding in place for cancer prevention efforts, I have championed legislation in Congress to facilitate increased research for several cancers. For example, lung cancer is the most prevalent cancer among men and women in the United States. One legislative response I have cosponsored is the Women and Lung Cancer Research and Preventive Services Act, which accelerates research into the prevention and treatment of lung cancer specifically for women. I'm also championing the Fairness for Kids with Cancer Act, which will provide funding for research to reduce childhood cancer rates across the country.

To all of the scientists, physicians, and others working in the medical research community across the country who have helped us make so much progress against cancer, I say, keep up the fight. I am encouraged by all the advances that have been made in cancer prevention, screening, early detection, diagnostics, and treatments, but we still have so far to go. I'm ready to partner with anyone who shares this common goal of ending cancer as we know it.

> ***I am encouraged by all the advances that have been made in cancer prevention, screening, early detection, diagnostics, and treatments, but we still have so far to go.***


U.S. HOUSE OF
REPRESENTATIVES

Introducing children to science and other educational programs early in life greatly enhances the likelihood that they will go on to earn higher degrees (663). The NIH Center to Reduce Cancer Health Disparities offers funding support for underrepresented minorities from middle school through the junior tenure-track faculty level 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 (664). Additionally, NIH sponsors the Science, Education, Partnership Awards (SEPA) Program, which facilitates collaborations between medical researchers and preK-12th grade teachers (665). Of the 351 participants in Q-Cubed, a University of Arizona's SEPA-sponsored high school program, 82 percent went on to attend college (666). These awards provide valuable early exposures to the world of medical research and showcase how rewarding a career in research can be.

Graduate students and postdoctoral fellows comprise the largest share of the academic research workforce. In addition to their advisors' grants, trainees are supported by a variety of institutional "T" awards, as well as individual "F" and "K" 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 targeted toward underrepresented minorities, while others, like the K99/R00 award, are designed to help bridge the gap between postdoctoral research and the establishment of a new independent laboratory. A study of 1,846 physician scientists (those with the dual MD-PhD degree) found that 63.8 percent of those who received an F30 or F31 grant during their training had a full-time faculty appointment within eight years of graduating, compared to 51.6 percent of those who did not receive an F30 or F31 grant (667). Another study found that 30.2–48.4 percent of post-doctoral fellows who received a K01, K08, K23, or K99 award scored an R01 independent research grant within seven years (668). These data suggest that identifying and supporting promising early-career researchers facilitate a successful transition to independent scientists.

NCI has also taken steps to support junior tenure-track research faculty. For example, NCI has created several programs and policies to help establish independent laboratories, including setting a payline in the 15th percentile for "early-stage investigators" (researchers within 10 years of completing their terminal degree), compared to 10 percent for the general applicant pool. In addition, the most meritorious NCI R01 applications from early-stage investigators can be converted to Method to Extend Research in Time (MERIT) R37 awards (669). This program, which began in 2018, extends grants up to seven years instead of five, allowing more time for new faculty to establish their laboratories before submitting renewal applications. Furthermore, the NIH Faculty Institutional Recruitment for Sustainable Transformation (FIRST) program supports innovative recruitment strategies at institutions with the goal of developing a critical mass of early-career faculty who have shown a demonstrated commitment to building a diverse research workforce (670).

As with other aspects of life, the COVID-19 pandemic has created enormous challenges for early-career researchers, including laboratories closing for months; long-term experiments being cancelled before they yielded results; and capacity limits reducing the availability of mentors and collaborators. Additionally, many universities halted the hiring of new junior tenure-track faculty due to financial constraints, creating a bottleneck in the research workforce pipeline with potentially devastating consequences. Early-career female scientists, especially those with young children, have been particularly impacted by the pandemic, highlighting the importance of focusing additional support for women in science (671–673). The influx of innovative ideas from young scientists is critical for future breakthroughs against cancer and other deadly diseases. As Congress considers both annual appropriations and supplemental funding, it will be vital to invest in additional resources to support early-career researchers.

Advancing Regulatory Science to Ensure the Safety and Efficacy of Medical Products

The role of FDA in ensuring the safety and efficacy of anticancer therapeutics is critical for medical research. As cutting-edge advances in research expand our arsenal against cancer, the agency must keep pace with innovation, while ensuring regulatory oversight over the growing number of therapeutics. Although user fee agreements are an essential source of support, congressionally appropriated funds are essential to the agency's mission. Discretionary funds support crucial regulatory science programs that generate evidence for the development of regulatory policies to accelerate the delivery of safe and effective anticancer therapeutics into the hands of patients.

FDA OCE was established in 2017 under the 21st Century Cures Act to facilitate the development of anticancer treatments and improve regulatory efficiency. OCE promotes collaborations among other FDA staff members with oncology expertise from the Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation (CBER), and Center for Devices and Radiological Health (CDRH).

OCE has also made important strides in accelerating regulatory review of anticancer therapeutics. The center's Real-Time Oncology Review (RTOR) Program was initiated in 2018 to jumpstart the review process of oncology products by facilitating earlier submission of data. During its first two years, RTOR supported the application submission and review of 20 oncology products, of which nine received breakthrough therapy designation and all received priority review (674). In 2019, Project Orbis was established for concurrent submission of drug approval applications for review by multiple international regulatory agencies to facilitate faster global adoption of new anticancer therapies. Over the course of its

first year, OCE approved 38 of the 60 marketing applications it received, and soon afterward many were approved abroad by foreign agencies (675).

Despite the unprecedented adversities caused by the COVID-19 pandemic, OCE has continued its critical work of reviewing anticancer therapeutics. This is demonstrated by the approval of 19 new anticancer therapeutics by the Center in 2020. In early 2021, OCE started Project Post COVIDity to develop partnerships with external experts and to study outcomes of patients with cancer infected with SARS-CoV-2 using real-world evidence generated from electronic health records, insurance claims data, and wearable health devices. In addition, Project Post COVIDity will analyze the impact of COVID-19 on patients with cancer, including effects on treatment delays, long-term COVID-19 symptoms, and therapeutic regimen selection (676). Project Post COVIDity also provides an important opportunity to inform clinical trial design and conduct for oncology drugs. Furthermore, Project Post COVIDity continues ongoing efforts of FDA to explore potential uses for real-world evidence in regulatory decision-making, as mandated by legislation including the 21st Century Cures Act.

REDUCING BARRIERS TO CLINICAL TRIAL PARTICIPATION

Participation in clinical trials drives improvements in overall survival for the represented diseases and demographics (677–679), and often results in better clinical outcomes for participants compared to nonparticipants (680–682). When adult patients with cancer are offered to join a trial, 55 percent accept (683). However, only 8 percent of adult patients with cancer (684), and 19.9 percent of pediatric and adolescent patients with cancer (685), enroll in clinical trials in the United States. While participation rates tend to be significantly higher at academic medical centers (684,686), the vast majority of patients with cancer never participate in trials. This is, in part, because more than 75 percent of patients with cancer are unable to join trials; either a trial is unavailable for their cancer type or they do not meet the eligibility criteria due to previous treatments or comorbidities (684). Additional barriers to participation include the lack of health care facilities in underserved areas, mistrust in the health care system, failure of physicians to offer clinical trials to patients, childcare needs, and the time and costs associated with traveling to study sites (687–691).

The COVID-19 pandemic greatly exacerbated the existing hurdles for clinical trials, but also made it necessary to implement long-sought approaches to address those challenges. In March 2020, FDA issued guidance outlining flexibilities in the conduct of clinical trials to help lessen the adverse effects of COVID-19 and trial sponsors quickly adopted them (692). Flexibilities included:

- Virtual visits to assess safety and clinical outcomes
- Delivering investigational products to the homes of participants
- Consenting participants remotely
- Collaborating with local physicians, laboratories, and imaging facilities

Such flexibilities have been recommended by FDA in the past, are popular with patients, decrease costs to participants, and may increase trial participation in the future if implemented permanently (also see sidebar on **Lessons from COVID-19 to Streamline Oncology Clinical Trials**, p. 78). FDA has ongoing engagement efforts with stakeholders to determine the path forward on increasing clinical trial accessibility and ease of participating while maintaining standards for patient safety and data integrity (390). In addition to these enhancements to clinical trials, many patients, clinicians, and advocacy groups recommend increased use of patient navigators to help connect patients with cancer to clinical trials (693–695). However, patient navigation often lacks sustainable payment models or insurance coverage (696).

FDA has also prioritized improving representation of racial, ethnic, and gender minorities in oncology clinical trials. Project Equity, launched by OCE in 2020, aims to improve evidence generation for underrepresented populations in trials by issuing guidance to industry to facilitate the accrual of diverse populations, fostering collaboration among stakeholders, and characterizing outcomes among underrepresented groups. Furthermore, CDER and CBER released voluntary guidance in November 2020 to encourage trial sponsors to implement strategies that would increase representation of racial and ethnic minorities (697), including:

- Broadening eligibility criteria for late-stage efficacy trials when more patients with comorbidities can be safely included;
- Detailing strategies to ensure trial participants reflect the diversity of the intended patient population of an investigational therapeutic or device;
- Encouraging trials or follow-up studies to include representation of racial and ethnic minorities, when possible, to definitively determine differences in safety and efficacy;
- Conducting trials at decentralized local health facilities while maintaining data integrity and patient safety; and
- Advancing the appropriate use of real-world evidence to fill evidence gaps where randomized clinical trials may not be feasible.

Recently, FDA has also taken actions to improve the availability of anticancer therapeutics for patients across all ages. In 2020, the agency initiated enforcement of key provisions in the Research to Accelerate Cures and Equity (RACE) for Children Act requiring certain targeted cancer therapies developed for adult patients to be studied in pediatric patients. In addition, FDA's Project Silver represents a global regulatory effort

Continued on page 148 ▸

U.S. REPRESENTATIVE FOR WISCONSIN'S 4TH DISTRICT | AGE 70

The Honorable Gwen Moore

Thank you for the opportunity to share about my experience as a cancer survivor. I hope in sharing my story I can help others who are experiencing the challenges that I did as I navigated this process.

I learned of my cancer diagnosis with small-cell lymphocytic lymphoma in the spring of 2018. I was quickly reassured by my doctors that I will survive, and this cancer will die with me but not be the death of me. Three years later the doctors were right; today I write this in great health and wellness.

Naturally, there was the initial anxiety of being diagnosed with cancer. On one hand the diagnosis was a relief since I had been going through weekly testing. On the other hand, I was scared. My fear was followed by the gratefulness that this cancer will not kill me. I cried tears of joy from realizing that I will have many more years of good health to love my family and serve my community. Then one day, when I was lying in bed undergoing chemo I thought: how different would my outlook be without medical research that helped develop the $15,000 a month drug that I now take?

Again, tears filled my eyes as I thought of those whose diagnoses would have been a death sentence. Immediately my mind raced back to those questions I had on the hospital bed three years ago.

Almost 2 million Americans are diagnosed with cancer annually. How many of those Americans are immediately reassured that they will survive? How many of those Americans will worry about the financial burden they will place on their families in the fight to survive? Every day people make the difficult decision to forgo treatment or ration their insulin or other lifesaving medications to avoid thousands in debt.

These questions should not have to be asked in a developed country such as ours. Hundreds of thousands of people should not be forced between the false dichotomy of physical survival and economic survival. My cancer diagnosis only empowered me to fight harder for the health care of those Americans who are not as fortunate as I am. That is why I am a perseverant defender of the Affordable Care Act and work to reduce the number of uninsured in our country.

To all the doctors, health care workers, and researchers working hard to find cures and treatment for cancer, please keep fighting to save American lives. I promise that I will fight until I cannot fight anymore to protect the millions of poor and working-class Americans living with cancer. I will relentlessly continue to support the medical research and innovation that will eradicate cancer.

> ***I will relentlessly continue to support the medical research and innovation that will eradicate cancer.***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to highlight drug development programs with indications particularly impacting older patients (75 and older) and promotes increased enrollment of geriatric patients in clinical trials for anticancer therapeutics.

Expanding Policy Opportunities in Cancer Prevention and Treatment

It is estimated that about 40 percent of cancer cases in the United States are attributable to preventable causes, such as tobacco use, HPV infection, and UV exposure, among others (see **Preventing Cancer: Identifying Risk Factors**, p. 36). Furthermore, screening for early detection makes it more likely that cancer can be intercepted, and patients treated successfully (see **Screening for Early Detection**, p. 55). A key hurdle to receiving preventive interventions and cancer screenings is coverage by insurance. A provision in the Affordable Care Act requires full insurance coverage of any preventive service recommended by U.S. Preventive Services Task Force (USPSTF). In May 2021, USPSTF updated its recommendation for Americans who should be screened for lung cancer. Previously, current and former smokers between the ages of 55 and 80, who smoked a pack a day for 30 years, were included in the recommendation. Under the new guidelines, smokers as young as 50 years old and those who smoked a pack a day for 20 years are recommended to receive annual screening free of charge through insurance. This expansion is expected to nearly double the number of smokers who should be screened, and it is particularly beneficial for women and African American smokers who tend to smoke fewer cigarettes on average compared to white men and yet have an elevated risk of developing lung cancer.

In May 2021, USPSTF addressed the sharp increase in colorectal cancer incidence among individuals under the age of 50 by lowering its age recommendation from 50 to 45 for initiating colorectal cancer screening for individuals at average risk for the disease. The new guidelines are expected to help identify more patients with colorectal cancer earlier when it is easier to treat. Additionally, USPSTF is currently reviewing the breast cancer screening guidelines (698).

Public health policies and programs play an important role in supporting equitable access to effective cancer prevention methods such as screening, early treatment, and HPV vaccinations. Every year in the United States, HPV infection accounts for about 35,900 cases of cancer, including almost all cases of cervical cancer (699). HPV vaccination is highly effective at preventing cancer (309) and is recommended for girls and boys age 11 or 12 years (See sidebar on **HPV Vaccination Recommendations**, p. 151). Unfortunately, HPV vaccination rates among U.S. adolescents have risen slowly in recent years; only 58.6 percent of eligible U.S. teens were fully vaccinated against HPV in 2020 (311), which is significantly below the national goal of 80 percent set by U.S. Department of Health and Human Services in Healthy People 2020 (700). Therefore, continued funding for screening programs such as CDC's National Breast and Cervical Cancer Early Detection Program is essential. The elimination of HPV-related cancers in the United States will only be possible through concerted efforts by all stakeholders to enhance public awareness of the importance of vaccination and to improve screening and treatment of precancerous HPV-related lesions.

The cancer advocacy and scientific communities continue to work with members of Congress, NCI, CDC, and other federal agencies to support and accelerate the elimination of HPV-related cancers in the United States and globally through public policy. State- and local-level vaccination mandates to attend public schools have greatly reduced the incidence of diseases like measles, mumps, and pertussis. However, only Hawaii, Rhode Island, Virginia, Puerto Rico, and Washington, DC, require HPV vaccination for school attendance. The states of Connecticut and New York have been pursuing similar bills to mandate HPV vaccines since 2020, but further efforts are needed to achieve the goal of an 80 percent vaccination rate in the United States.

REDUCING TOBACCO-RELATED ILLNESS THROUGH PUBLIC HEALTH POLICY

Tobacco use in the United States is at a historic low due to effective tobacco control policies and smoking awareness campaigns since the 1960s. In 2019, 20.8 percent of U.S. adults regularly used any tobacco product (23), reflecting the fact that the majority of adult smokers have successfully quit smoking; 20.9 percent of all adults in 2018 were former smokers (200). Unfortunately, 23.6 percent of high school students used tobacco products in 2020, the vast majority of whom used flavored e-cigarettes (701,702). This epidemic of nicotine dependence among youth threatens to reverse the progress made against tobacco-related illnesses. Furthermore, despite successes in reducing adult tobacco use, tobacco remains the number one preventable cause of cancer, highlighting the importance of additional tobacco control policies to prevent and cure all tobacco-related cancers.

In February 2020, FDA implemented a ban on all flavored pod and cartridge-based e-cigarettes, except for tobacco and menthol flavors. Open-tank and single-use e-cigarettes were also exempted from any flavor restrictions, leaving thousands of appealing flavors on the market. As a result, there was a more than 1,000 percent increase from 2019 to 2020 (2.4 vs. 26.6 percent) in the number of high school students who vape using disposable e-cigarettes (216). With more than 80 percent of youth e-cigarette users vaping flavored products, loopholes that allow flavored tobacco products should be eliminated. Additionally, manufacturers of e-cigarettes, cigars, and other deemed tobacco products that were on the market as of August 8, 2016, were required to submit Premarket Tobacco Product Applications (PMTA) to FDA by September 9, 2020. FDA received more than 6 million PMTAs by the deadline. FDA will determine which products comply with regulations and whether scientific evidence submitted by manufacturers proves that their products meet the statutory level of being "appropriate for the protection of public health."

In April 2021, the Biden administration announced its intent to ban menthol cigarettes, as well as menthol and other flavors in mass-produced cigars. This development was welcomed by public health organizations, including AACR, that have advocated for this policy for nearly 10 years. FDA plans to develop rules and regulations on menthol cigarettes and flavored cigars by the end of 2021. Numerous studies have shown that menthol flavoring makes it easier for smokers to get addicted to cigarettes, results in greater nicotine exposure, and makes it harder to quit smoking than nonflavored combustible cigarettes (703–708). For years, the tobacco industry has targeted and advertised menthol cigarettes to communities of color with devastating results that have driven tobacco-related health disparities (709). Menthol also contributes to youth initiation of tobacco products, and about half of all high school smokers use menthol, according to a new study (216). A recent report estimates that banning menthol would prevent 630,000 tobacco-related deaths over the next 40 years, of which more than one third will be among African Americans (710).

The Biden administration is also considering issuing a product standard to restrict the nicotine content in cigarettes to less addictive levels (711). Modeling data suggest that lowering nicotine to minimally addictive levels could result in 5 million smokers quitting within a year, and 13 million smokers quitting within five years; the projected smoking rate among U.S. adults would decrease to 1.4 percent by 2060 as a result (712).

Other potential actions to protect public health include prohibiting the sale of all flavored tobacco products, such as disposable and open-tank e-cigarettes commonly used by youth; supporting strong action by FDA's Center for Tobacco Products to regulate the manufacturing, distribution, and marketing of tobacco products; and increasing funding for the prevention and cessation activities that are supported by CDC's Office on Smoking and Health.

Accelerating Progress Against Pediatric Cancer

Cancer is the leading cause of disease-related deaths among children ages 1-14, and the second leading cause of death overall. Thanks to advances in cancer treatments over the last few decades, the 5-year survival rate for childhood cancer has increased to over 84 percent (713) (see **Figure 2**, p. 12). However, there are many types of childhood 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 secondary effects of childhood cancer (see **Challenges Faced by Cancer Survivors**, p. 121). Policies that encourage the development of new treatments for childhood cancers—and those that support survivors of childhood cancers—are critical to ensuring the best outcomes for every child impacted by cancer.

In 2018, Congress passed the Childhood Cancer Survivorship, Treatment, Access, and Research (STAR) Act, the most comprehensive childhood cancer legislation to date. This law contains numerous provisions to improve data collection, tracking, and survivorship support related to childhood cancers, and many of these items are being implemented, including:

- Grants awarded by NCI to support and expand the collection of biospecimens from children, adolescents, and young adults diagnosed with cancer;
- The expansion of childhood cancer surveillance programs at CDC, made possible by the development of a new cloud-based data reporting system;
- NCI-supported research on childhood cancer survivorship, including an emphasis on late effects of pediatric cancer treatment, disparities in outcomes for pediatric patients, and barriers to follow-up care;
- A report from the Government Accountability Office (GAO) entitled *Survivors of Childhood Cancer: Factors Affecting Access to Follow-up Care* (released July 2020);
- A series of reports from the Agency for Healthcare Research and Quality (AHRQ), including *Disparities and Barriers to Pediatric Cancer Survivorship Care* (released March 2021) and *Models of Care That Include Primary Care for Adult Survivors of Childhood Cancer: A Realist Review* (released May 2021); and
- A mandate to include at least one pediatric oncologist on the National Cancer Advisory Board.

Congress has consistently appropriated $30 million per year in funding as authorized by the STAR Act. Continued full appropriations will be essential to realizing the potential of this landmark childhood cancer law. Additionally, 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, as well as to implement recommendations highlighted in GAO and AHRQ reports.

The Childhood Cancer Data Initiative (CCDI) is another program designed to improve the collection and sharing of data related to pediatric cancers, with the goal to better understand cancer biology specific to children and ultimately to improve prevention, treatment, quality of life, and survivorship. CCDI is complementary to the work that NCI is leading on biorepositories under the STAR Act. CCDI funding is proposed for a total of 10 years from FY 2020 to FY 2029, with $50 million to be allocated each year, and Congress fully funded the initiative in both FY 2020 and FY 2021. NCI has granted CCDI funds for childhood cancers and research activities and has engaged the entire childhood cancer community in the implementation of the initiative.

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, it is challenging to establish clinical trials only for pediatric cancers with specific mutations, 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 strong potential of 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. The RACE Act requires that drug manufacturers study molecularly targeted therapeutics developed for adult cancer patients in pediatric populations with the same mutations. In response to these provisions, FDA has developed a Pediatric Molecular Target List to provide guidance to companies as they plan for new drug and biologic submissions (714). As of August 18, 2020, applications submitted to FDA for therapies that meet the RACE Act criteria must have agency-approved pediatric study plans.

The Gabriella Miller Kids First Pediatric Research Program (Kids First) at NIH is supporting new discoveries in understanding the biology of childhood cancers and their links to birth defects. Funding for this program was established in the Gabriella Miller Kids First Research Act, passed by Congress in 2014. Since then, over $75 million has been invested in pediatric research through the program. The bipartisan Gabriella Miller Kids First Research Act 2.0 was introduced in the House in January 2021 by Reps. Jennifer Wexton (D-VA), Tom Cole (R-OK), Peter Welch (D-VT), and Gus Bilirakis (R-FL), and a companion bill was introduced in the Senate by Sens. Tim Kaine (D-VA), Jerry Moran (R-KS), Mark Warner (D-VA), and Bill Cassidy (R-LA). This legislation 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.

Children with cancer are among those most impacted by drug shortages, which are largely driven by economic factors and occur primarily in the United States. This issue was brought into focus in the summer of 2019 when a shortage of vincristine—a chemotherapeutic agent that is an essential component of treatments for many childhood cancers—caused delays in treatment and forced pediatric oncologists to consider rationing the short supply of the drug that was available (715). Even though the vincristine shortage was eventually resolved, it highlighted the fragile nature of the supply chain for many drugs, and particularly those for the treatment of childhood cancers. In October 2019, FDA issued a report titled *Drug Shortages: Root Causes and Potential Solutions* (716), which includes the following recommendations:

- Creating a shared understanding of the impact of drug shortages on patients and the contracting practices that may contribute to shortages;
- Developing a rating system to incentivize drug manufacturers to invest in quality management maturity for their facilities; and
- Promoting sustainable private sector contracts (e.g., with payers, purchasers, and group purchasing organizations) to make sure there is a reliable supply of medically important drugs.

Addressing Cancer Health Disparities

Medically underserved populations experience poorer health outcomes due to systemic disadvantages. Centuries of policies that restrict housing, educational, and employment opportunities for racial and ethnic minorities have led to lower health insurance rates, lower utilization of preventive health services, and poor nutrition. Additionally, an under-representation 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. Over the past year, policy developments related to cancer screening, clinical trial participation, nutrition, and health insurance have demonstrated that progress in addressing cancer health disparities is possible.

Unequal access to cancer screening contributes to cancer health disparities. In the past, USPSTF had received criticism for underrepresentation of racial and ethnic minorities in the clinical studies that the task force used to develop cancer screening guidelines for average risk individuals (717). Consequently, the existing guidelines were more likely to identify cancers in white patients while missing many cases in underserved racial and ethnic minorities. In an effort to address disparities in cancer screening, USPSTF recently revisited its guidelines for lung and colorectal cancers (see **Cancer Screening Guidelines**, p. 60), as well as for Hepatitis B infection, which can cause liver cancer (26,718,719). The new guidelines greatly expand the number and diversity of people who can now receive these cancer screening tests at no cost. Furthermore, CDC's National Breast and Cervical Cancer Early Detection Program provides 139,000 low-income and uninsured women with annual access to screening, diagnostic, and treatment services for breast and cervical cancer (720).

Food insecurity is a key driver of health disparities and contributes to worse cancer outcomes as well as to obesity, a major risk factor for cancer, due to limited access to healthy food options (721). With widespread job losses during the COVID-19 pandemic, there was a fear that the prevalence of food insecurity would dramatically increase. Therefore, Congress included increased unemployment and nutritional support benefits in COVID-19 relief bills in March 2020, December 2020, and March 2021 (722,723). Increases to nutrition benefits included the Supplemental Nutrition Assistance Program (SNAP); Special Supplemental Nutrition Program for Women, Infants, and Children (WIC); The Emergency Food Assistance Program (TEFAP); and support

to provide free meals to low-income children who would qualify for free school lunches. Increases to SNAP benefits alone provided roughly an extra $27 per month per beneficiary through September 2021, helping feed families during the pandemic. CDC programs like the Racial and Ethnic Approaches to Community Health also fund local public health efforts, such as promoting exercise and ensuring underserved communities have access to fresh fruit and vegetables (724).

Lack of health insurance coverage is another major contributor to health disparities, as highlighted by **Congresswoman Gwen Moore** (see p. 146), with 30 million uninsured Americans in early 2020 (725). 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 states that have expanded Medicaid coverage, uninsured rates have decreased by nearly half compared to states that have not expanded Medicaid (726). Medicaid expansion has been particularly beneficial for young adult cancer survivors (727), who have seen dramatic increases in the ability to afford health care and are therefore less likely to skip medications or delay refills. Over the past year, Nebraska and Oklahoma joined 35 other states in expanding Medicaid. Additionally, Missouri voters approved Medicaid expansion via ballot referendum in August 2020, but implementation is on hold while the expansion faces legal challenges (728). Medicaid has been a crucial safety net during the COVID-19 pandemic as unemployed Americans lost workplace health insurance plans. The number of Medicaid beneficiaries grew by 7.6 million between February 2020 and November 2020 (729). Furthermore, Congress passed the CLINICAL TREATMENT Act as part of the fiscal year 2021 federal spending bill, which requires Medicaid to cover the routine medical costs of patients enrolled in clinical trials. The CLINICAL TREATMENT Act greatly enhances the ability of Medicaid beneficiaries to enroll in trials.

Several programs run by NIH, NCI, the National Institute on Minority Health and Health Disparities (NIMHD), and CDC are designed to address cancer health disparities. For example, NIH's All of Us program, funded by the 21st Century Cures Act, aims to improve precision medical research by increasing representation of racial and ethnic minorities. NIMHD is NIH's core institute to support research on the many factors that cause disparate health outcomes, including socioeconomics, politics, discrimination, culture, and environment. Unfortunately, NIMHD has an even lower RPG success rate than NCI, funding fewer than 8 percent of investigator-initiated grants (655). The NCI Community Oncology Research Program is a national network that helps connect community health facilities to clinical trials at NCI-designated cancer centers. Additionally, the NCI Center to Reduce Cancer Health Disparities supports disparities research within NCI and reinforces training a diverse cancer research workforce. CDC's National Program of Cancer Registries is essential for understanding the scope of cancer disparities by tracking cancer rates all over the United States.

Informing Policy Through Patient Advocacy

Patient advocacy organizations work tirelessly to educate, promote awareness, support, and raise funds for cancer research. Dating back to 1938, when the 75th Congress passed House Joint Resolution 468, "To dedicate the month of April in each year to a voluntary national program for the control of cancer," awareness days and months have become valuable tools to rally the community and engage Capitol Hill. As of 2021, there are 70 officially recognized annual awareness events in support of cancer. For example, in May 2021, AACR spearheaded the effort to recognize May as National Cancer Research Month. Senator Dianne Feinstein (D-CA) and Senator Shelley Moore Capito (R-WV) sponsored S. Res. 253 to designate May as National Cancer Research Month, which recognized the importance of cancer research and acknowledged the efforts of cancer researchers (730). In addition to the Senate resolution, AACR received a Presidential Message from President Biden recognizing May as National Cancer Research Month (731).

In addition to congressional resolutions, patient advocacy organizations bring thousands of advocates to Washington, DC, to engage Capitol Hill in advocacy "Hill Days". Hill Days provide an organization's membership the opportunity to meet members of Congress, share the goals and mission of their organization, and ask members of Congress to introduce or support legislation beneficial to their community of researchers, clinicians, and patient advocates. Patient advocates are essential participants as they personalize the disease and issues related to the disease and provide members of Congress with critical information to influence their policy decisions. According to congressional staffers, in-person visits from constituents are the most influential way to communicate with a senator or representative who is undecided on an issue.

In 2020, the move to virtual platforms expanded access for constituents to engage with legislators outside of Washington, DC, but also created barriers for policy makers and advocates to develop relationships. Legislators cited the lack of face-to-face interactions with patient advocates as the biggest challenge they encountered when they needed to gain information on an issue. (732,733).

INCREASING PATIENT ADVOCATE ENGAGEMENT WITH FDA, NCI, AND ACADEMIA

Well-organized patient advocates have a positive influence in cancer research, drug development, and legislation. Nonprofit patient advocacy groups have demonstrated the power to significantly improve research outcomes (734). A meaningful patient advocacy strategy has become an important part of the mission for many cancer research organizations (735). Meaningful engagement with patient advocates is necessary

PATIENT ADVOCACY ORGANIZATION

A patient advocacy organization is a nonprofit entity that has pledged to help patients with a particular disease, disability, or condition. This assistance excludes direct care but can involve research education, raising awareness, and lobbying to support or oppose policies, regulations, drug approvals or government funding decisions. There is a continuum of patient advocacy organizations from large, established organizations with sizeable budgets run by boards of directors, to organizations led by a small group of volunteers raising money to fund research. All share the common goal to improve health outcomes for patients.

for clinical trial design and conduct, ensuring the relevance and prioritization of research questions, identification of opportunities and barriers to accrual, success and transparency of research activities, dissemination of findings into practice, and broader understanding of the disease.

Patient advocacy is rooted in the right of all people to be informed and have as much participation and control as possible over their health care decisions. It expanded into research and policy following the AIDS (Acquired Immune Deficiency Syndrome) activist movement; broader visibility and understanding of the disease forced pharmaceutical industries, the United States government, and regulatory agencies to open a dialogue with patient advocates, allocate funding, and expedite a response to the epidemic. Encouraged by their success, other health-related organizations have developed alliances between scientists, clinicians, and patient advocates. These highly productive dialogues are advancing scientific discourse and fueling research advocacy in both private and public sectors at local, regional, and national levels.

Today, patient advocates have a substantial role in the development and regulatory review of potentially life-changing treatments at FDA and NCI.

In addition to patient advocacy organizations, many professional societies, health systems, and organizations recognize the need to encourage greater engagement between scientists and the general public. Starting in 2012, NCI-designated Comprehensive Cancer Centers were required to include proposals for community engagement in their core grant applications, which helped create valuable new relationships with their communities (736). Adding to this established engagement framework, the COVID-19 pandemic created a large demand for up-to-date and easy to understand health information. In response, numerous health systems across the United States hosted regular webinars to understand the concerns of their communities and explain the latest public health guidance (737–739). Professional societies and scientific journals also provided unprecedented open access to peer-reviewed articles and organized a wide range of conference sessions and forums. These heightened community engagement efforts provide effective models to continue outreach for other important public health issues following the pandemic.

Many young scientists also recognize the importance of engaging with the public and are taking the initiative to create communication resources. In the past ten years, the number of active graduate student and postdoctoral science policy and communication organizations at U.S. universities increased from just a small handful to nearly 50 in 2020 (740). These student-run organizations are leading the way in providing training and communication and public engagement for hundreds of early-career researchers. Additionally, some universities have created courses and other opportunities for PhD students to learn from patients and clinicians and to participate in tumor boards (741). The enthusiasm of early-career researchers brings promise for the future of engagement between patients and scientists.

"We embrace a culture of advocacy at NCI because we know how important the patient perspective is in developing thoughtful cancer care. Research advocates give patients a voice at NCI—they remind us why and for whom we are doing this work."

Norman E. Sharpless, MD; NCI Director

Supporting Patients with Cancer During the COVID-19 Pandemic

Patient advocacy organizations did not slow operations during the COVID-19 pandemic. Communities collaborated to share information and combat misinformation; educational programs focusing on the coronavirus, vaccines, and clinical trials were released weekly; and financial assistance resources were created for patients with cancer. Furthermore, advocates united to support timely access to the COVID-19 vaccine, promote inclusion in clinical trials, highlight health inequities, and mitigate the adverse impact of COVID-19 on cancer screenings and care. A survey by the National Coalition for Cancer Survivorship highlighted the increased need for these programs as patients with cancer reported heightened feelings of anxiety and excessive worry due to COVID-19 (742). Eighty-five percent of the families surveyed had lost their jobs

or had a reduction in work hours, and 25 percent experienced a delay in treatment or follow-up care. Fortunately, virtual programs were widely adopted for support groups, remote visits for care, and research, thereby expanding opportunities for outreach and engagement.

As programs increased, many walks, runs, and other cancer-specific fundraising events were cancelled or saw a decline in participation and charitable revenue. According to the Giving USA 2021 Annual Report, donations to health organizations were estimated to have declined by 3.0 percent (4.2 percent adjusted for inflation) in a year when charitable giving in the United States reached an all-time high. This funding shortage strained many patient advocacy organizations which were asked to do more with less money and fewer staff members. The long-term implications for cancer research funding are still unclear. Each year, private and nonprofit patient advocacy organizations award millions of dollars to fuel progress in cancer research. Cancer researchers rely on this steady stream of funding to advance their discoveries from the laboratory to the patient and are grateful for the continued support from the thousands of patient advocates committed to funding cancer research. In the wake of the COVID-19 pandemic, support for cancer research is even more important to ensure continued progress in discovering new and innovative treatments.

THE AACR CALL TO ACTION

The extraordinary advances against cancer detailed in this report were made possible by the dedicated 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, making it possible to prevent, detect, diagnose, treat, and cure many types of cancer that previously lacked effective treatment options. These advances are driving down overall U.S. cancer incidence and death rates and increasing the number of individuals who are surviving longer after a cancer diagnosis.

Thanks to the remarkable bipartisan efforts of Congress, NIH funding has increased by nearly $13 billion or 42 percent from FY 2015 to FY 2021. These significant investments make it possible for researchers across the country to continue making advances against cancer and many other diseases.

Despite this progress, much more work needs to be done on behalf of those living with cancer and those who will be diagnosed in the future. For example, there are still no effective treatments for many of the over 200 known types of cancer. Furthermore, the COVID-19 pandemic has had a profoundly negative impact on medical research and cancer care, bringing many critical projects to a halt, delaying screening and treatments, and diverting resources to the immediate need of responding to COVID-19. The adverse consequences of the COVID-19 pandemic will be felt for years and perhaps decades to come.

As the United States recovers from the devastating toll of the COVID-19 pandemic, we are reminded of the enormous value of medical research in overall public health. Decades of investment in basic, translational, and clinical research have enabled scientists to develop diagnostics, treatments, and vaccines for this novel disease at a pace never seen before. This robust approach to medical research has already saved hundreds of thousands of lives from COVID-19 in the United States alone. Cancer researchers were uniquely positioned to respond to the challenges posed by COVID-19 and have played a vital role in combating the pandemic while continuing their quest to cure cancer. With so many promising opportunities ahead of us it is critical that we maintain our momentum of progress against cancer.

AACR deeply appreciates the commitment of Congress to expediting progress against cancer and other diseases through robust funding increases for NIH, as well as to supporting the critical regulatory science work at FDA and public health programs of CDC.

Therefore, AACR urges Congress to:

- Continue to support robust, sustained, and predictable growth for NIH and NCI by providing increases in their FY 2022 base budgets of at least $3.2 billion and $1.1 billion, respectively, for a total funding level of $46.4 billion for NIH and $7.6 billion for NCI.
- Ensure that the funding designated through the 21st Century Cures Act for targeted initiatives, including the National Cancer Moonshot, is fully appropriated in FY 2022 and is supplemental to the overall increase in the NIH base budget.
- Provide at least $10 billion for NIH in emergency supplemental funding to restart research and clinical trials that have been put on hold due to the pandemic, as proposed in the Research Investment to Spark the Economy (RISE) Act of 2021.
- Provide $50 million for the third year of the Childhood Cancer Data Initiative and no less than $30 million for the continued implementation of the Childhood Cancer STAR Act.
- Support 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.
- Support FDA's critical regulatory science initiatives and advance the development and regulation of oncology products by providing an increase of at least $343 million in discretionary budget authority in FY 2022, as recommended in President Biden's budget proposal.
- Support vital CDC Cancer Prevention and Control Programs with total funding of at least $559 million. This includes funding for comprehensive cancer control, cancer registries, and screening and awareness programs for specific cancers.

If we hope to reach the day when cancer is no longer a major health threat to our nation's citizens, Congress must provide robust, sustained, and predictable annual funding increases for NIH, NCI, FDA, and CDC in FY 2022 and beyond. These investments will help us transform cancer care, increase survivorship, spur economic growth, and maintain the position of the United States as a global leader in scientific and medical research and specifically in cancer research. Most importantly this will continue to bring lifesaving cures to the millions of people worldwide whose lives are touched by cancer.

REFERENCES

1. Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer statistics, 2021. CA Cancer J Clin 2021;71:7–33.
2. Weinhouse S. National Cancer Act of 1971 - an editorial. Cancer Res 1972;32:i–ii.
3. American Cancer Society. Cancer facts & figures 2021. Atlanta, Ga: American Cancer Society; 2021.
4. Surveillance, Epidemiology, and End Results (SEER) Program. Available from: https://seer.cancer.gov/.
5. Steliarova-Foucher E, Stiller C, Lacour B, Kaatsch P. International classification of childhood cancer, third edition. Cancer 2005;103:1457–67.
6. American Cancer Society. Cancer facts & figures 2014. Atlanta, GA: American Cancer Society; 2014.
7. Bade BC, Dela Cruz CS. Lung cancer 2020: epidemiology, etiology, and prevention. Clin Chest Med 2020;41:1–24.
8. Durham AL, Adcock IM. The relationship between COPD and lung cancer. Lung Cancer 2015;90:121–7.
9. Samet JM. Tobacco smoking: the leading cause of preventable disease worldwide. Thorac Surg Clin 2013;23:103–12.
10. Stanhope BJ, Burdette WJ, Cochran WG, Farber E, Fieser LF, Furth J, et al. Smoking and health: report of the Advisory Committee to the Surgeon General of the Public Health Service. U.S. Department of Health, Education, and Welfare; Public Health Service Publication No. 1103. Washington (DC): U.S. Government Printing Office; 1964.
11. Office of the Surgeon General, U.S. Department of Health and Human Services. . Tobacco reports and publications. 2021 [updated 2020 Jan 23; cited 2021 Mar 5]. Available from: https://www.hhs.gov/surgeongeneral/reports-and-publications/tobacco/index.html.
12. Centers for Disease Control and Prevention. Current cigarette smoking among adults in the United States. 2020 [updated 2020 Dec 10; cited 2021 March 5]. Available from : https://www.cdc.gov/tobacco/data_statistics/fact_sheets/adult_data/cig_smoking/index.htm.
13. Institute of Medicine (US) Committee on Secondhand Smoke Exposure and Acute Coronary Events. Secondhand smoke exposure and cardiovascular effects: making sense of the evidence. Washington (DC): National Academies Press; 2012.
14. Substance Abuse and Mental Health Services Administration. About the Synar Amendment and Program. 1992 [updated 2021 Aug 11; cited 2021 Mar 5]. Available from: https://www.samhsa.gov/synar/about-synar.
15. U.S. Food & Drug Administration.. Tobacco 21. 2019 [updated 2021 Feb 22; cited 2021 Mar 5]. Available from: https://www.fda.gov/tobacco-products/retail-sales-tobacco-products/tobacco-21.
16. Henry BJ. Impact of tobacco-control legislation. Clin J Oncol Nurs 2013;17:195–200.
17. Community intervention trial for smoking cessation (COMMIT): II. Changes in adult cigarette smoking prevalence. Am J Public Health 1995;85:193–200.
18. Community intervention trial for smoking cessation (COMMIT): I. Cohort results from a four-year community intervention. Am J Public Health 1995;85:183–92.
19. Stillman FA, Hartman AM, Graubard BI, Gilpin EA, Murray DM, Gibson JT. Evaluation of the American Stop Smoking Intervention Study (ASSIST): a report of outcomes. J Natl Cancer Inst 2003;95:1681–91.
20. Roeseler A, Meaney M, Riordan M, Solomon M, Herndon S, Hallett C. NCI's state and community research initiative: a model for future tobacco control research. Tob Control 2016;25:i1–3.
21. Meza R, Jimenez-Mendoza E, Levy DT. Trends in tobacco use among adolescents by grade, sex, and race, 1991-2019. JAMA Netw Open 2020;3:e2027465.
22. National Center for Chronic Disease Prevention and Health Promotion (US) Office on Smoking and Health. The health consequences of smoking—50 years of progress: a report of the Surgeon General. Atlanta (GA): Centers for Disease Control and Prevention (US); 2014.
23. Cornelius ME, Wang TW, Jamal A, Loretan CG, Neff LJ. Tobacco product use among adults — United States, 2019. MMWR Morb Mortal Wkly Rep 2020;69:1736–42.
24. Henley SJ, Ward EM, Scott S, Ma J, Anderson RN, Firth AU, et al. Annual report to the nation on the status of cancer, part I: national cancer statistics. Cancer 2020;126:2225–49.
25. Gridelli C, Rossi A, Carbone DP, Guarize J, Karachaliou N, Mok T, et al. Non-small-cell lung cancer. Nat Rev Dis Prim 2015;1:15009.
26. Jonas DE, Reuland DS, Reddy SM, Nagle M, Clark SD, Weber RP, et al. Screening for lung cancer with low-dose computed tomography: updated evidence report and systematic review for the US Preventive Services Task Force. JAMA 2021;325:971-87.
27. Suzuki Y, Orita M, Shiraishi M, Hayashi K, Sekiya T. Detection of ras gene mutations in human lung cancers by single-strand conformation polymorphism analysis of polymerase chain reaction products. Oncogene 1990;5:1037–43.
28. Graziano SL, Gamble GP, Newman NB, Abbott LZ, Rooney M, Mookherjee S, et al. Prognostic significance of K-ras codon 12 mutations in patients with resected stage I and II non-small-cell lung cancer. J Clin Oncol 1999;17:668–75.
29. Mitsudomi T, Viallet J, Mulshine JL, Linnoila RI, Minna JD, Gazdar AF. Mutations of ras genes distinguish a subset of non-small-cell lung cancer cell lines from small-cell lung cancer cell lines. Oncogene 1991;6:1353–62.
30. Nelson MA, Wymer J, Clements N Jr. Detection of K-ras gene mutations in non-neoplastic lung tissue and lung cancers. Cancer Lett 1996;103:115–21.
31. Riely GJ, Marks J, Pao W. KRAS mutations in non-small cell lung cancer. Proc Am Thorac Soc 2009;6:201–5.
32. Ding L, Getz G, Wheeler DA, Mardis ER, McLellan MD, Cibulskis K, et al. Somatic mutations affect key pathways in lung adenocarcinoma. Nature 2008;455:1069–75.
33. Lynch TJ, Bell DW, Sordella R, Gurubhagavatula S, Okimoto RA, Brannigan BW, et al. Activating mutations in the epidermal growth factor receptor underlying responsiveness of non–small-cell lung cancer to gefitinib. N Engl J Med 2004;350:2129–39.
34. Paez JG, Jänne PA, Lee JC, Tracy S, Greulich H, Gabriel S, et al. EGFR mutations in lung cancer: correlation with clinical response to gefitinib therapy. Science 2004;304:1497–500.
35. Kobayashi S, Boggon TJ, Dayaram T, Jänne PA, Kocher O, Meyerson M, et al. EGFR mutation and resistance of non–small-cell lung cancer to gefitinib. N Engl J Med 2005;352:786–92.
36. Weiss J, Sos ML, Seidel D, Peifer M, Zander T, Heuckmann JM, et al. Frequent and focal FGFR1 amplification associates with therapeutically tractable FGFR1 dependency in squamous cell lung cancer. Sci Transl Med 2010;2:62ra93.

REFERENCES

37. Soda M, Choi YL, Enomoto M, Takada S, Yamashita Y, Ishikawa S, et al. Identification of the transforming EML4-ALK fusion gene in non-small-cell lung cancer. Nature 2007;448:561–6.

38. Lipson D, Capelletti M, Yelensky R, Otto G, Parker A, Jarosz M, et al. Identification of new ALK and RET gene fusions from colorectal and lung cancer biopsies. Nat Med 2012;18:382–4.

39. Rikova K, Guo A, Zeng Q, Possemato A, Yu J, Haack H, et al. Global survey of phosphotyrosine signaling identifies oncogenic kinases in lung cancer. Cell 2007;131:1190–203.

40. Ju YS, Lee WC, Shin JY, Lee S, Bleazard T, Won JK, et al. A transforming KIF5B and RET gene fusion in lung adenocarcinoma revealed from whole-genome and transcriptome sequencing. Genome Res 2012;22:436–45.

41. Kohno T, Ichikawa H, Totoki Y, Yasuda K, Hiramoto M, Nammo T, et al. KIF5B-RET fusions in lung adenocarcinoma. Nat Med 2012;18:375–7.

42. Takeuchi K, Soda M, Togashi Y, Suzuki R, Sakata S, Hatano S, et al. RET, ROS1 and ALK fusions in lung cancer. Nat Med 2012;18:378–81.

43. Wolf J, Seto T, Han JY, Reguart N, Garon EB, Groen HJM, et al. Capmatinib in MET Exon 14–mutated or MET -amplified non–small-cell lung cancer. N Engl J Med 2020;383:944–57.

44. Santarpia M, Massafra M, Gebbia V, D'Aquino A, Garipoli C, Altavilla G, et al. A narrative review of MET inhibitors in non-small cell lung cancer with MET exon 14 skipping mutations. Transl Lung Cancer Res 2021;10:1536–56.

45. Vaishnavi A, Capelletti M, Le AT, Kako S, Butaney M, Ercan D, et al. Oncogenic and drug-sensitive NTRK1 rearrangements in lung cancer. Nat Med 2013;19:1469–72.

46. Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. Cell 2011;144:646–74.

47. Nicholson LB. The immune system. Essays Biochem 2016;60:275–301.

48. Buchbinder EI, Desai A. CTLA-4 and PD-1 pathways: similarities, differences, and implications of their inhibition. Am J Clin Oncol 2016;39:98–106.

49. Reckamp KL. Advances in immunotherapy for non–small cell lung cancer. Clin Adv Hematol Oncol 2015;13:847–53.

50. Pardoll DM. The blockade of immune checkpoints in cancer immunotherapy. Nat Rev Cancer 2012;12:252–64.

51. Qiu Z, Chen Z, Zhang C, Zhong W. Achievements and futures of immune checkpoint inhibitors in non-small cell lung cancer. Exp Hematol Oncol 2019;8:19.

52. Yuan M, Huang LL, Chen JH, Wu J, Xu Q. The emerging treatment landscape of targeted therapy in non-small-cell lung cancer. Signal Transduct Target Ther 2019;4:61.

53. Da Cunha Santos G, Shepherd FA, Tsao MS. EGFR mutations and lung cancer. Annu Rev Pathol Mech Dis 2011;6:49–69.

54. Iams WT, Porter J, Horn L. Immunotherapeutic approaches for small-cell lung cancer. Nat Rev Clin Oncol 2020;17:300–12.

55. Fan YS. Companion diagnostic testing for targeted cancer therapies: an overview. Genet Test Mol Biomarkers 2013;17:515–23.

56. Gupta R, Othman T, Chen C, Sandhu J, Ouyang C, Fakih M. Guardant360 circulating tumor DNA assay is concordant with FoundationOne next-generation sequencing in detecting actionable driver mutations in anti-EGFR naive metastatic colorectal cancer. Oncologist 2020;25:235–43.

57. Islami F, Ward EM, Sung H, Ma J, Anderson RN, Firth AU, et al. Annual report to the nation on the status of cancer, part 1: national cancer statistics. Cancer 2021;126:2225–49.

58. Rahib L, Wehner MR, Matrisian LM, Nead KT. Estimated projection of US cancer incidence and death to 2040. JAMA Netw Open 2021;4:e214708.

59. Hodi FS, O'Day SJ, McDermott DF, Weber RW, Sosman JA, Haanen JB, et al. Improved survival with ipilimumab in patients with metastatic melanoma. N Engl J Med 2010;363:711–23.

60. American Cancer Society. Cancer facts & figures 2017. Atlanta: American Cancer Society; 2017.

61. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2021;71:209–49.

62. COVID-19 hits cancer research funding. Cancer Discov 2020;10:756.

63. Zon L, Gomes AP, Cance WG, Ribas A, Tuveson D, Postel-Vinay S, et al. Impact of COVID-19 pandemic on cancer research. Cancer Cell 2020;38:591–3.

64. Kamath SD, Kircher SM, Benson AB. Comparison of cancer burden and nonprofit oganization funding reveals disparities in funding across cancer types. J Natl Compr Cancer Netw 2019;17:849–54.

65. Birkmeyer JD, Barnato A, Birkmeyer N, Bessler R, Skinner J. The impact of the COVID-19 pandemic on hospital admissions in the United States. Health Aff 2020;39:2010–7.

66. Patt D, Gordan L, Diaz M, Okon T, Grady L, Harmison M, et al. Impact of COVID-19 on cancer care: how the pandemic is delaying cancer diagnosis and treatment for American seniors. JCO Clin Cancer Inform 2020;(4):1059–71.

67. American Hospital Association. Hospitals and health systems face unprecedented financial pressures due to COVID-19. 2020 May [cited 2021 Aug 9]. Available from: https://www.aha.org/guidesreports/2020-05-05-hospitals-and-health-systems-face-unprecedented-financial-pressures-due.

68. Lamont EB, Diamond SS, Katriel RG, Ensign LL, Liu J, Rusli E, et al. Trends in oncology clinical trials launched before and during the COVID-19 pandemic. JAMA Netw Open 2021;4:e2036353.

69. Marcum M, Kurtzweil N, Vollmer C, Schmid L, Vollmer A, Kastl A, et al. COVID-19 pandemic and impact on cancer clinical trials: an academic medical center perspective. Cancer Med 2020;9:6141–6.

70. Ribas A, Sengupta R, Locke T, Zaidi SK Campbell KM, Carethers JM, et al. Priority COVID-19 vaccination for patients with cancer while vaccine supply is limited. Cancer Discov 2021;11:233–6.

71. Sng CCT, Wong YNS, Wu A, Ottaviani D, Chopra N, Galazi M, et al. Cancer history and systemic anti-cancer therapy independently predict COVID-19 mortality: a UK tertiary hospital experience. Front Oncol 2020;10:595804.

72. Cattaneo C, Daffini R, Pagani C, Salvetti M, Mancin V, Borlenghi E, et al. Clinical characteristics and risk factors for mortality in hematologic patients affected by COVID-19. Cancer 2020;126:5069–76.

73. Meng Y, Lu W, Guo E, Liu J, Yang B, Wu P, et al. Cancer history is an independent risk factor for mortality in hospitalized COVID-19 patients: a propensity score-matched analysis. J Hematol Oncol 2020;13:75.

REFERENCES

74. Mehta V, Goel S, Kabarriti R, Cole D, Goldfinger M, Acuna-Villaorduna A, et al. Case fatality rate of cancer patients with COVID-19 in a New York hospital system. Cancer Discov 2020;10:935–41.

75. Rüthrich MM, Giessen-Jung C, Borgmann S, Classen AY, Dolff S, Grüner B, et al. COVID-19 in cancer patients: clinical characteristics and outcome - an analysis of the LEOSS registry. Ann Hematol 2020;100:383–93.

76. Lunski MJ, Burton J, Tawagi K, Maslov D, Simenson V, Barr D, et al. Multivariate mortality analyses in COVID-19: comparing patients with cancer and patients without cancer in Louisiana. Cancer 2021;127:266–74.

77. Tian J, Yuan X, Xiao J, Zhong Q, Yang C, Liu B, et al. Clinical characteristics and risk factors associated with COVID-19 disease severity in patients with cancer in Wuhan, China: a multicentre, retrospective, cohort study. Lancet Oncol 2020;21:893–903.

78. Dai M, Liu D, Liu M, Zhou F, Li G, Chen Z, et al. Patients with cancer appear more vulnerable to SARS-CoV-2: a multicenter study during the COVID-19 outbreak. Cancer Discov 2020;10:783–91.

79. Yang L, Chai P, Yu J, Fan X. Effects of cancer on patients with COVID-19: a systematic review and meta-analysis of 63,019 participants. Cancer Biol Med 2021;18:298–307.

80. Wang QQ, Berger NA, Xu R. Analyses of risk, racial disparity, and outcomes among US patients with cancer and COVID-19 infection. JAMA Oncol 2020;7:220–7.

81. Garassino MC, Whisenant JG, Huang LC, Trama A, Torri V, Agustoni F, et al. COVID-19 in patients with thoracic malignancies (TERAVOLT): first results of an international, registry-based, cohort study. Lancet Oncol 2020;21:914–22.

82. Lara OD, O'Cearbhaill RE, Smith MJ, Sutter ME, Knisely A, McEachron J, et al. COVID-19 outcomes of patients with gynecologic cancer in New York City. Cancer 2020;126:4294–303.

83. Van Haren RM, Delman AM, Turner KM, Waits B, Hemingway M, Shah, SA, et al. Impact of the COVID-19 pandemic on lung cancer screening program and subsequent lung cancer. J Am Coll Surg 2020;232:600–5.

84. Xu Y, Liu H, Hu K, Wang M. Clinical management of lung cancer patients during the outbreak of 2019 novel coronavirus disease (COVID-19). Chinese J Lung Cancer 2020;23:136–41.

85. Hultcrantz M, Richter J, Rosenbaum CA, Patel D, Smith EL, Korde N, et al. COVID-19 infections and clinical outcomes in patients with multiple myeloma in New York City: a cohort study from five academic centers. Blood Cancer Discov 2020;1:234–43.

86. Williamson EJ, Walker AJ, Bhaskaran K, Bacon S, Bates C, Morton CE, et al. Factors associated with COVID-19-related death using OpenSAFELY. Nature 2020;584:430–6.

87. Wang QQ, Berger NA, Xu R. When hematologic malignancies meet COVID-19 in the United States: Infections, death and disparities. Blood Rev 2020;47:100775.

88. Elmore LW, Greer SF, Daniels EC, Saxe CC, Melner MH, Krawiec GM, et al. Blueprint for cancer research: critical gaps and opportunities. CA Cancer J Clin 2020;71:107–39.

89. Zugazagoitia J, Guedes C, Ponce S, Ferrer I, Molina-Pinelo S, Paz-Ares L. Current challenges in cancer treatment. Clin Ther 2016;38:1551–66.

90. National Cancer Institute. Cancer health disparities definitions. Available from: https://www.cancer.gov/about-nci/organization/crchd/about-health-disparities/definitions.

91. Sengupta R, Honey K. AACR cancer disparities progress report 2020 : achieving the bold vision of health equity for racial and ethnic minorities and other underserved populations. Cancer Epidemiol Biomarkers Prev 2020;29:1843.

92. American Cancer Society. Cancer facts & figures for African Americans 2019-2021. Atlanta: American Cancer Society; 2021.

93. Melkonian SC, Weir HK, Jim MA, Preikschat B, Haverkamp D, White MC. Incidence and trends of the leading cancers with elevated incidence among American Indian and Alaska Native populations, 2012–2016. Am J Epidemiol. 2020;190:529–38.

94. Zahnd WE, Gomez SL, Steck SE, Brown MJ, Ganai S, Zhang J, et al. Rural-urban and racial/ethnic trends and disparities in early-onset and average-onset colorectal cancer. Cancer 2020;127:239–48.

95. Boehmer U, Gereige J, Winter M, Ozonoff A, Scout N. Transgender individuals' cancer survivorship: results of a cross-sectional study. Cancer 2020;126:2829–36.

96. Moss JL, Pinto CN, Srinivasan S, Cronin KA, Croyle RT. Persistent poverty and cancer mortality rates: an analysis of county-level poverty designations. Cancer Epidemiol Biomarkers Prev 2020;29:1949–54.

97. Berrian JL, Liu Y, Lian M, Schmaltz CL, Colditz GA. Relationship between insurance status and outcomes for patients with breast cancer in Missouri. Cancer 2020;127:931–7.

98. Zavala VA, Bracci PM, Carethers JM, Carvajal-Carmona L, Coggins NB, Cruz-Correa MR, et al. Cancer health disparities in racial/ethnic minorities in the United States. Br J Cancer 2021;124:315–32.

99. Miller JW, Plescia M, Ekwueme DU. Public health national approach to reducing breast and cervical cancer disparities. Cancer 2014;120(Suppl 16):2537–9.

100. Adler NE, Newman K. Socioeconomic disparities in health: pathways and policies. Health Aff 2002;21:60–76.

101. Freedman JA, Abo M Al, Allen TA, Piwarski SA, Wegermann K, Patierno SR. Biological aspects of cancer health disparities. Annu Rev Med 2021;72:229–41.

102. Newman LA. Cascading consequences of systemic racism on public health. Ann Surg 2021;273:10–12.

103. WHO report on cancer: setting priorities, investing wisely and providing care for all. Geneva: World Health Organization; 2020. Licence: CC BY-NC-SA 3.0 IGO.

104. 2017 National Population Projections Datasets [Internet]. U.S. Census Bureau. Washington, DC. 2017. Available from : https://www.census.gov/data/datasets/2017/demo/popproj/2017-popproj.html.

105. Scott AR, Stoltzfus KC, Tchelebi LT, Trifiletti DM, Lehrer EJ, Rao P, et al. Trends in cancer incidence in US adolescents and young adults, 1973-2015. JAMA Netw Open 2020;3:e2027738.

106. Siegel RL, Torre LA, Soerjomataram I, Hayes RB, Bray F, Weber TK, et al. Global patterns and trends in colorectal cancer incidence in young adults. Gut 2019;68:2179–85.

107. Bleyer A, Spreafico F, Barr R. Prostate cancer in young men: an emerging young adult and older adolescent challenge. Cancer 2020;126:46–57.

108. Codipilly DC, Sawas T, Dhaliwal L, Johnson JL, Lansing R, Wang KK, et al. Epidemiology and outcomes of young-onset esophageal adenocarcinoma: an analysis from a population-based database. Cancer Epidemiol Biomarkers Prev 2020;30:142–9.

REFERENCES

109. Siegel RL, Miller KD, Goding Sauer A, Fedewa SA Butterly LF, Anderson JC, et al. Colorectal cancer statistics, 2020. CA Cancer J Clin 2020;70:145–64.

110. Gopal S, Sharpless NE. Cancer as a Global Health Priority. JAMA. 2021;326(9):809–810.

111. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018;68:394–424.

112. United Nations Development Programme. Human development report 2020. New York: United Nations; 2020.

113. Wikipedia contributors. Developing country. Wikipedia, The Free Encyclopedia. July 22, 2004, at 10:55 UTC. Available at: https://en.wikipedia.org/wiki/Developing_country - Accessed August 25, 2021. https://en.wikipedia.org/wiki/Developing_country

114. Hall MT, Simms KT, Lew JB, Smith MA, Brotherton JM, Saville M, et al. The projected timeframe until cervical cancer elimination in Australia: a modelling study. Lancet Public Health 2019;4:e19-e27.

115. Brisson M, Kim JJ, Canfell K, Drolet M, Gingras G, Burger EA, et al. Impact of HPV vaccination and cervical screening on cervical cancer elimination: a comparative modelling analysis in 78 low-income and lower-middle-income countries. Lancet 2020;395:575-590.

116. Wells JC, Sharma S, Del Paggio JC, Hopman WM, Gyawali B, Mukherji D, et al. An Analysis of Contemporary Oncology Randomized Clinical Trials From Low/Middle-Income vs High-Income Countries. JAMA Oncol 2021;7:379-385.

117. National Cancer Institute. NCI Priorities in Reducing Global Cancer Burden. -. [updated 2020 Sep 24; cited August 25, 2021. Available from: https://www.cancer.gov/news-events/cancer-currents-blog/2020/cancer-global-reducing-burden-satish-gopal

118. American Cancer Society Cancer Action Network. The costs of cancer: 2020 edition. 2020. Available from: https://www.fightcancer.org/sites/default/files/National Documents/Costs-of-Cancer-2020-10222020.pdf.

119. By the numbers: NCI budget breakdown, FY 2018. Cancer Discov 2019;9:160.

120. Mariotto AB, Enewold L, Zhao J, Zeruto CA, Robin Yabroff K. Medical care costs associated with cancer survivorship in the United States. Cancer Epidemiol Biomarkers Prev 2020;29:1304–12.

121. Zafar SY. Financial toxicity of cancer care: it's time to intervene. J Natl Cancer Inst 2016;108:djv370.

122. Rosenbaum L. The untold toll - the pandemic's effects on patients without COVID-19. N Engl J Med 2020;382:2368–71.

123. Lander ES, Linton LM, Birren B, Nusbaum C, Zody MC, Baldwin J, et al. Initial sequencing and analysis of the human genome. Nature 2001;409:860–921.

124. American Association for Cancer Research. AACR Cancer Progress Report 2011: transforming patient care through innovation. Available from: https://www.celebrationofscience.org/assets/Uploads/AACRCancerProgressReport2011.pdf.

125. Collins FS, Anderson JM, Austin CP, Battey JF, Birnbaum LS, Briggs JP, et al. Basic science: bedrock of progress. Science 2016;351:1405.

126. Cleary EG, Beierlein JM, Khanuja NS, McNamee LM, Ledley FD. Contribution of NIH funding to new drug approvals 2010–2016. Proc Natl Acad Sci U S A 2018;115:2329–34.

127. Quinn JJ, Jones MG, Okimoto RA, Nanjo S, Chan MM, Yosef N, et al. Single-cell lineages reveal the rates, routes, and drivers of metastasis in cancer xenografts. Science 2021;371:eabc1944.

128. Ubellacker JM, Tasdogan A, Ramesh V, Shen B, Mitchell EC, Martin-Sandoval MS, et al. Lymph protects metastasizing melanoma cells from ferroptosis. Nature 2020;585:113–8.

129. American Association for Cancer Research. AACR Cancer Progress Report 2014. Clin Cancer Res 2014;20(Supplement 1):S1–S112.

130. Lee Y, Bogdanoff D, Wang Y, Hartoularos GC, Woo JM, Mowery CT, et al. Xyzeq: spatially resolved single-cell RNA sequencing reveals expression heterogeneity in the tumor microenvironment. Sci Adv 2021;7:eabg4722.

131. Dentro SC, Leshchiner I, Haase K, Tarabichi M, Wintersinger J, Deshwar AG, et al. Characterizing genetic intra-tumor heterogeneity across 2,658 human cancer genomes. Cell 2021;184:2239–54.

132. De Jonge MM, De Kroon CD, Jenner DJ, Oosting J, de Hullu JA, Mourits MJE, et al. Endometrial cancer risk in women with germline BRCA1 or BRCA2 mutations: multicenter cohort study. J Natl Cancer Inst 2021 Mar 12 [Epub ahead of print].

133. Tlemsani C, Takahashi N, Pongor L, Rajapakse VN, Tyagi M, Wen X, et al. Whole-exome sequencing reveals germline-mutated small cell lung cancer subtype with favorable response to DNA repair-targeted therapies. Sci Transl Med 2021;13:eabc7488.

134. Samadder NJ, Riegert-Johnson D, Boardman L, Rhodes D, Wick M, Okuno S, et al. Comparison of universal genetic testing vs guideline-directed targeted testing for patients with hereditary cancer syndrome. JAMA Oncol 2021;7:230–7.

135. Susswein LR, Marshall ML, Nusbaum R, Vogel Postula KJ, Weissman SM, Yackowski L, et al. Pathogenic and likely pathogenic variant prevalence among the first 10,000 patients referred for next-generation cancer panel testing. Genet Med 2016;18:823–32.

136. Cobain EF, Wu YM, Vats P, Chugh R, Worden F, Smith DC, et al. Assessment of clinical benefit of integrative genomic profiling in advanced solid tumors. JAMA Oncol 2021;7:525–33.

137. Huang KL, Mashl RJ, Wu Y, Ritter DI, Wang J, Oh C, et al. Pathogenic germline variants in 10,389 adult cancers. Cell 2018;173:355–70.

138. Grivennikov SI, Greten FR, Karin M. Immunity, inflammation, and cancer. Cell 2010;140:883–99.

139. American Association for Cancer Research. AACR Cancer Progress Report 2015. Clin Cancer Res 2015;21(Supplement 1):S1–S128.

140. Cieslik M, Chinnaiyan AM. Global genomics project unravels cancer's complexity at unprecedented scale. Nature 2020;578:39–40.

141. ICGC/TCGA Pan-Cancer Analysis of Whole Genomes Consortium. Pan-cancer analysis of whole genomes. Nature 2020;578:82–93.

142. Alexandrov LB, Kim J, Haradhvala NJ, Huang MN, Ng AWT, Wu Y, et al. The repertoire of mutational signatures in human cancer. Nature 2020;578:94–101.

143. Gerstung M, Jolly C, Leshchiner I, Dentro SC, Gonzalez S, Rosebrock D, et al. The evolutionary history of 2,658 cancers. Nature 2020;578:122–8.

144. Bach K, Pensa S, Zarocsinceva M, Kania K, Stockis J, Pinaud S, et al. Time-resolved single-cell analysis of Brca1 associated mammary tumourigenesis reveals aberrant differentiation of luminal progenitors. Nat Commun 2021;12:1502.

145. Breast Cancer Association Consortium, Dorling L, Carvalho S, Allen J, Gonzalez-Neira A, Luccarini C, et al. Breast cancer risk genes - association analysis in more than 113,000 women. N Engl J Med 2021;384:428–39.

REFERENCES

146. Hu C, Hart SN, Gnanaolivu R, Huang H, Lee KY, Na J, et al. A population-based study of genes previously implicated in breast cancer. N Engl J Med 2021;384:440–51.

147. Fiala EM, Jayakumaran G, Mauguen A, Kennedy JA, Bouvier N, Kemel Y, et al. Prospective pan-cancer germline testing using MSK-IMPACT informs clinical translation in 751 patients with pediatric solid tumors. Nat Cancer 2021;2:357–65.

148. Feusier JE, Arunachalam S, Tashi T, Baker MJ, VanSant-Webb C, Ferdig A, et al. Large-scale Identification of clonal hematopoiesis and mutations recurrent in blood cancers. Blood Cancer Discov 2021;2:226–37.

149. Fantini MC, Guadagni I. From inflammation to colitis-associated colorectal cancer in inflammatory bowel disease: pathogenesis and impact of current therapies. Dig Liver Dis 2021;53:558–65.

150. Jiang Q, Isquith J, Ladel L, Mark A, Holm F, Mason C, et al. Inflammation-driven deaminase deregulation fuels human pre-leukemia stem cell evolution. Cell Rep 2021;34:108670.

151. Rozenblatt-Rosen O, Regev A, Oberdoerffer P, Nawy T, Hupalowska A, Rood JE, et al. The Human Tumor Atlas Network: charting tumor transitions across space and time at single-cell resolution. Cell 2020;181:236–49.

152. Tilston-Lunel A, Mazzilli S, Kingston NM, Sqymaniak AD, Hicks-Berthet J, Kern JG, et al. Aberrant epithelial polarity cues drive the development of precancerous airway lesions. Proc Natl Acad Sci U S A 2021;118:e2019282118.

153. Dawson MA. The cancer epigenome: concepts, challenges, and therapeutic opportunities. Science 2017;355:1147–52.

154. Chung C, Sweha SR, Pratt D, Tamrazi B, Panwalkar P, Banda A, et al. Integrated metabolic and epigenomic reprograming by H3K27M mutations in diffuse intrinsic pontine gliomas. Cancer Cell 2020;38:334–9.

155. Sroka MW, Vakoc CR. An epigenetic tipping point in cancer comes under the microscope. Nature 2021;590:399–400.

156. Landry LG, Ali N, Williams DR, Rehm HL, Bonham VL. Lack Of diversity in genomic databases is a barrier to translating precision medicine research into practice. Health Aff 2018;37:780–5.

157. Sirugo G, Williams SM, Tishkoff SA. The missing diversity in human genetic studies. Cell 2019;177:26–31.

158. Zewdu A, Casadei L, Pollock RE, Braggio D. Adipose tumor microenvironment. Adv Exp Med Biol 2020;1226:73–86.

159. Hawkins ED, Duarte D, Akinduro O, Khorshed RA, Passaro D, Nowicka M, et al. T-cell acute leukaemia exhibits dynamic interactions with bone marrow microenvironments. Nature 2016;538:518–22.

160. McGranahan N, Swanton C. Clonal heterogeneity and tumor evolution: past, present, and the future. Cell 2017;168:613–28.

161. Feig C, Gopinathan A, Neesse A, Chan DS, Cook N, Tuveson DA. The pancreas cancer microenvironment. Clin Cancer Res 2012;18:4266–76.

162. Khalaf K, Hana D, Chou JTT, Singh C, Mackiewicz A, Kaczmarek M. Aspects of the tumor microenvironment involved in immune resistance and drug resistance. Front Immunol 2021;12:656364.

163. Chen Y, Kim J, Yang S, Wang H, Wu CJ, Sugimoto H, et al. Type I collagen deletion in αSMA+ myofibroblasts augments immune suppression and accelerates progression of pancreatic cancer. Cancer Cell 2021;39:548–65.

164. Lim SA, Wei J, Nguyen TLM, Shi H, Su W, Palacios G, et al. Lipid signalling enforces functional specialization of Treg cells in tumours. Nature 2021;591:306–11.

165. Swanton C. Take lessons from cancer evolution to the clinic. Nature 2020;581:382–3.

166. Casanova-Acebes M, Dalla E, Leader AM, LeBerichel J, Nikolic J, Morales BM, et al. Tissue-resident macrophages provide a pro-tumorigenic niche to early NSCLC cells. Nature 2021;595:578-84.

167. Joshi K, de Massy MR, Ismail M, Reading JL, Uddin I, Woolston A, et al. Spatial heterogeneity of the T cell receptor repertoire reflects the mutational landscape in lung cancer. Nat Med 2019;25:1549–59.

168. Abjul Jabbar K, Ahmed Raza SE, Rosenthal R, Jamal-Hanjani M, Veeriah S, Akarca A, et al. Geospatial immune variability illuminates differential evolution of lung adenocarcinoma. Nat Med 2020;26:1054–62.

169. Lopez S, Lim EL, Horswell S, Haase K, Huebner A, Dietzen M, et al. Interplay between whole-genome doubling and the accumulation of deleterious alterations in cancer evolution. Nat Genet 2020;52:283–93.

170. Rosenthal R, Larose Cadieux E, Salgado R, Al Bakir M, Moore DA, Hiley CT, et al. Neoantigen-directed immune escape in lung cancer evolution. Nature 2019;567:479–85.

171. Ghorani E, Reading JL, Henry JY, de Massy MR, Rosenthal R, Turati V, et al. The T cell differentiation landscape is shaped by tumour mutations in lung cancer. Nat Cancer 2020;1:546–61.

172. American Association for Cancer Research. AACR Cancer Progress Report 2016. Clin Cancer Res 2016;22(Supplement 1):S1–S137.

173. Wheeler DA, Takebe N, Hinoue T, Hoadley KA, Cardenas MF, Hamilton AM, et al. Molecular features of cancers exhibiting exceptional responses to treatment. Cancer Cell 2021;39:39:38–53.

174. Howlader N, Forjaz G, Mooradian MJ, Meza R, Kong CY, Cronin KA, et al. The effect of advances in lung-cancer treatment on population mortality. N Engl J Med 2020;383:640–9.

175. Pishvaian MJ, Blais EM, Brody JR, Lyons E, DeArbeloa P, Hendifar A, et al. Overall survival in patients with pancreatic cancer receiving matched therapies following molecular profiling: a retrospective analysis of the Know Your Tumor registry trial. Lancet Oncol 2020;21:508–518.

176. Sicklick JK, Kato S, Okamura R, Schwaederle M, Hahn ME, Williams CB, et al. Molecular profiling of cancer patients enables personalized combination therapy: the I-PREDICT study. Nat Med 2019;25:744–50.

177. Lee JS, Nair NU, Dinstag G, Chapman L, Chung Y, Wang K, et al. Synthetic lethality-mediated precision oncology via the tumor transcriptome. Cell 2021;184:2487–502.

178. Davar D, Dzutsev AK, McCulloch JA, Rodrigues RR, Chauvin JM, Morrison RM, et al. Fecal microbiota transplant overcomes resistance to anti-PD-1 therapy in melanoma patients. Science 2021;371:595–602.

179. Kaiser J. Special diets might boost the power of drugs to vanquish cancers. Science 2021 Apr 1. Available from: https://www.sciencemag.org/news/2021/04/special-diets-might-boost-power-drugs-vanquish-cancers.

180. Zhu M, Wang T, Huang Y, Zhao X, Ding Y, Zhu M, et al. Genetic risk for overall cancer and the benefit of adherence to a healthy lifestyle. Cancer Res 2021 Jul 28 [Epub ahead of print].

REFERENCES

181. Islami F, Goding Sauer A, Miller KD, Siegel RL, Fedewa SA, Jacobs EJ, et al. Proportion and number of cancer cases and deaths attributable to potentially modifiable risk factors in the United States. CA Cancer J Clin 2018;68:31–54.

182. Sung H, Hyun N, Leach CR, Yabroff KR, Jemal A. Association of first primary cancer with risk of subsequent primary cancer among survivors of adult-onset cancers in the United States. JAMA 2020;324:2521–35.

183. Petrelli F, Cortellini A, Indini A, Tomasello G, Ghidini M, Nigro O, et al. Association of obesity with survival outcomes in patients with cancer. JAMA Netw Open 2021;4:e213520.

184. Sengupta R, Honey K. AACR cancer progress report 2018: harnessing research discoveries for patient benefit. Clin Cancer Res 2018;24:4351.

185. Islami F, Bandi P, Sahar L, Ma J, Drope J, Jemal A. Cancer deaths attributable to cigarette smoking in 152 U.S. metropolitan or micropolitan statistical areas, 2013–2017. Cancer Causes Control 2021;32:311–6.

186. Trust for America's Health. The state of obesity 2020: better policies for a healthier America. Robert Wood Johnson Foundation. 2020 Sept. Available from: https://www.tfah.org/report-details/state-of-obesity-2020/.

187. Sung H, Siegel RL, Rosenberg PS, Jemal A. Emerging cancer trends among young adults in the USA: analysis of a population-based cancer registry. Lancet Public Health 2019;4:e137–47.

188. Koroukian SM, Dong W, Berger NA. Changes in age distribution of obesity-associated cancers. JAMA Netw Open 2019;2:e199261.

189. Avery CL, Howard AG, Nichols HB. Comparison of 20-year obesity-associated cancer mortality trends with heart disease mortality trends in the US. JAMA Netw Open 2021;4:e218356.

190. Shastri SS, Talluri R, Shete S. Disparities in secondhand smoke exposure in the United States: National Health and Nutrition Examination Survey 2011-2018. JAMA Intern Med 2021;181:134–7.

191. The state of childhood obesity - helping all children grow up healthy. Robert Wood Johnson Foundation. [updated 2020 Oct; cited 2021 Jul 10]. Available from: https://stateofchildhoodobesity.org/.

192. Department of Public Health, City of Philadelphia. Neighborhood food retail in Philadelphia. 2019 Sep. Available from: https://www.phila.gov/media/20190923114738/GHP_FoodAccessRpt_Final_wDate.pdf.

193. Bandi P, Minihan AK, Siegel RL, Islami F, Nargis N, Jemal A, et al. Updated review of major cancer risk factors and screening test use in the United States in 2018 and 2019, with a focus on smoking cessation. Cancer Epidemiol Biomarkers Prev 2021:30:1287–99.

194. Centers for Disease Conrol and Prevention. Viral hepatitis surveillance - United States. [cited 2021 Jul 10]. Available from: https://www.cdc.gov/hepatitis/statistics/SurveillanceRpts.htm.

195. American Lung Association. Key findings: state of the air. [cited 2021 Jul 10]. Available from: https://www.lung.org/research/sota/

196. American Lung Association. State of tobacco control 2021. [cited 2021 Jul 10]. Available from: https://www.lung.org/research/sotc.

197. Centers for Disease Control and Prevention. Cancer and tobacco use. CDC Vital Signs, November 2016. Available from: https://www.cdc.gov/vitalsigns/cancerandtobacco/index.html.

198. Vaz M, Hwang SY, Kagiampakis I, Phallen J, Patil A, O'Hagan HM, et al. Chronic cigarette smoke-induced epigenomic changes precede sensitization of bronchial epithelial cells to single-step transformation by KRAS mutations. Cancer Cell 2017;32:360–76.

199. Barrow TM, Klett H, Toth R, Bohm J, Gigic B, Habermann N, et al. Smoking is associated with hypermethylation of the APC 1A promoter in colorectal cancer: the ColoCare Study. J Pathol 2017;243:366–75.

200. United States Public Health Services Office of the Surgeon General; National Center for Chronic Disease Prevention and Health Promotion (US) Office on Smoking and Health. Smoking cessation: a report of the Surgeon General. Washington (DC); US Department of Health and Human Services; 2020.

201. U.S. Department of Health and Human Services. The health consequences of smoking – 50 years of progress: a report of the Surgeon General. Atlanta, GA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, 2014.

202. Gentzke AS, Wang TW, Jamal A, Park-Lee E, Ren C, Cullen KA, et al. Tobacco product use among middle and high school students — United States, 2020. MMWR Morb Mortal Wkly Rep 2020;69:1881–8.

203. Pérez A, N'Hpang RS, Callahan E, Bluestein M, Kuk AE, chen B, et al. Age at initiation of cigarette use in a nationally representative sample of US youth, 2013-2017. JAMA Netw Open 2021;4:e210218.

204. Barrington-Trimis JL, Braymiller JL, Unger JB, Bluestein M, Kuk AE, Chen B, et al. Trends in the age of cigarette smoking initiation among young adults in the US from 2002 to 2018. JAMA Netw Open 2020;3:e210218.

205. GBD 2019 Tobacco Collaborators. Spatial, temporal, and demographic patterns in prevalence of smoking tobacco use and attributable disease burden in 204 countries and territories, 1990–2019: a systematic analysis from the Global Burden of Disease Study 2019. Lancet 2021;397:2337–60.

206. Drouin O, Sato R, Drehmer JE, Nabi-Burza E, Walters BH, Winickoff JP, et al. Cost-effectiveness of a smoking cessation Intervention for parents in pediatric primary care. JAMA Netw Open 2021;4:e213927.

207. Luk TT, Lam TH, Leung WC, Leung KY, Cheung KW, Kwa C, et al. Brief advice, nicotine replacement therapy sampling, and active referral for expectant fathers who smoke cigarettes: a randomized clinical trial. JAMA Intern Med 2021;181:1081–9.

208. Nabi-Burza E, Drehmer JE, Walters BH, Rigotti NA, Ossip DJ, Levy DE, et al. Treating parents for tobacco use in the pediatric setting: The Clinical Effort Against Secondhand Smoke Exposure Cluster Randomized Clinical Trial. JAMA Pediatr 2019;173:931–9.

209. Patnode CD, Henderson JT, Coppola EL, Melnikow J, Durbin S, Thomas RG. Interventions for tobacco cessation in adults, including pregnant persons: updated evidence report and systematic review for the US Preventive Services Task Force. JAMA 2021;325:280–98.

210. US Preventive Services Task Force, Krist AH, Davidson KW, Mangione CM, Barry MJ, Cabana M, et al. Interventions for tobacco smoking cessation in adults, including pregnant persons. JAMA 2021;325:265–79.

211. Christensen CH, Rostron B, Cosgrove C, Altekruse SF, Hartman AM, Gibson JT, et al. Association of cigarette, cigar, and pipe use with mortality risk in the US population. JAMA Intern Med 2018;178:469–76.

212. U.S. Department of Health and Human Services. Surgeon General's advisory on e-cigarette use among youth. Atlanta, GA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, 2016.

213. U.S. Department of Health and Human Services. E-cigarette use among youth and young adults. A report of the Surgeon General. Atlanta, GA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, 2016.

214. National Academies of Sciences, Engineering, and Medicine; Health and Medicine Division; Board on Population Health and Public Health Practice; Committee on the Review of the Health Effects of Electronic Nicotine Delivery Systems. Eaton DL, Kwan LY, Stratton K, editors. Public health consequences of e-cigarettes. Washington (DC): National Academies Press (US); 2018 Jan 23.

215. Wang TW, Gentzke AS, Neff LJ, Glidden EV, Jamal A, Park-Lee E, et al. Characteristics of e-cigarette use behaviors among US youth, 2020. JAMA Netw Open 2021;4:e2111336.

216. Gentzke AS, Wang TW, Jamal A, Park-Lee E, Ren C, Neff LJ, et al. E-cigarette use among middle and high school students — United States, 2020. MMWR Morb Mortal Wkly Rep 2020;69:1310–2.

217. Friedman AS, Xu S. Associations of flavored e-cigarette uptake with subsequent smoking initiation and cessation. JAMA Netw Open 2020;3:e203826.

218. Pierce JP, Chen R, Leas EC, White MM, Kealey S, Stone MD, et al. Use of e-cigarettes and other tobacco products and progression to daily cigarette smoking. Pediatrics 2021;147:e2020025122.

219. U.S. Food & Drug Adminstration. Some e-cigarette users are having seizures, most reports involving youth and young adults. [updated 2019 Apr 10; cited 2021 Jul 10]. Available from: https://www.fda.gov/tobacco-products/ctp-newsroom/some-e-cigarette-users-are-having-seizures-most-reports-involving-youth-and-young-adults.

220. Ellington S, Salvatore PP, Ko J, Danielson M, Kim L, Cyrus A, et al. Update: product, substance-use, and demographic characteristics of hospitalized patients in a nationwide outbreak of e-cigarette, or vaping, product use–associated lung injury — United States, August 2019–January 2020. MMWR Morb Mortal Wkly Rep 2020;69:44–9.

221. Chatham-Stephens K, Roguski K, Jang Y, Cho P, Jatlaoui TC, Kabbani S, et al. Characteristics of hospitalized and nonhospitalized patients in a nationwide outbreak of e-cigarette, or vaping, product use–associated lung injury — United States, November 2019. MMWR Morb Mortal Wkly Rep 2019;68:1076–80.

222. Adkins SH, Anderson KN, Goodman AB, Twentyman E, Danielson ML, Kimball A, et al. Demographics, substance use behaviors, and clinical characteristics of adolescents with e-cigarette, or vaping, product use-associated lung injury (EVALI) in the United States in 2019. JAMA Pediatr 2020;174:e200756.

223. Centers for Disease Control and Prevention. CDC Newsroom. CDC, states update number of hospitalized EVALI cases and EVALI deaths. 2020 Feb 25. Available from: https://www.cdc.gov/media/releases/2020/s0225-EVALI-cases-deaths.html.

224. Heinzerling A, Armatas C, Karmarkar E, Attfield K, Guo W, Wang Y, et al. Severe lung injury associated with use of e-cigarette, or vaping, products-California, 2019. JAMA Intern Med 2020;180:861–9.

225. Navon L, Jones CM, Ghinai I, King BA, Briss PA, Hacker KA, et al. Risk factors for e-cigarette, or vaping, product use–associated lung injury (EVALI) among adults who use e-cigarette, or vaping, products — Illinois, July–October 2019. MMWR Morb Mortal Wkly Rep 2019;68:1034–9.

226. Xie W, Kathuria H, Galiatsatos P, Blaha MJ, Hamburg NM, Robertson RM, et al. Association of electronic cigarette use with incident respiratory conditions among US adults from 2013 to 2018. JAMA Netw Open 2020;3:e2020816.

227. Caporale A, Langham MC, Guo W, Johncola A, Chatterjee S, Wehrli FW. Acute effects of electronic cigarette aerosol inhalation on vascular function detected at quantitative MRI. Radiology 2019;293:97–106.

228. Bhatta DN, Glantz SA. Association of e-cigarette use with respiratory disease among adults: a longitudinal analysis. Am J Prev Med 2020;58:182–90.

229. Bjurlin MA, Matulewicz RS, Roberts TR, Dearing BA, Schatz D, Sherman S, et al. Carcinogen Biomarkers in the Urine of Electronic Cigarette Users and Implications for the Development of Bladder Cancer: A Systematic Review. Eur Urol Oncol. 2020; S2588-9311:30029-8.

230. World Health Organization. WHO report on the global tobacco epidemic 2021: addressing new and emerging products. 2021 Jul 27. Available from: https://www.who.int/publications/i/item/9789240032095.

231. Gaiha SM, Lempert LK, Halpern-Felsher B. Underage youth and young adult e-cigarette use and access before and during the coronavirus disease 2019 pandemic. JAMA Netw Open 2020;3:e2027572.

232. Smith TT, Nahhas GJ, Carpenter MJ, Squeglia LM, Diaz VA, Leventhal AM, et al. Intention to quit vaping among United States adolescents. JAMA Pediatr 2021;175:97–9.

233. Graham AL, Amato MS, Cha S, Jacobs MA, Bottcher MM, Papandonatos GD. Effectiveness of a vaping cessation text message program among young adult e-cigarette users: a randomized clinical trial. JAMA Intern Med 2021;181:923–30.

234. Bennett M, Hair EC, Liu M, Pitzer L, Rath JM, Vallone DM. Exposure to tobacco content in episodic programs and tobacco and E-cigarette initiation. Prev Med 2020;139:106169.

235. Mayer M, Reyes-Guzman C, Grana R, Choi K, Freedman ND. Demographic characteristics, cigarette smoking, and e-cigarette use among US adults. JAMA Netw Open 2020;3:e2020694.

236. Everard CD, Silveira ML, Kimmel HL, Marshall D, Blanco C, Compton WM. Association of electronic nicotine delivery system use with cigarette smoking relapse among former smokers in the United States. JAMA Netw Open 2020;3:e204813.

237. Piercy KL, Troiano RP, Ballard RM, Carson SA, Fulton JE, Galuska DA, et al. The physical activity guidelines for Americans. JAMA 2018;320:2020–8.

238. Matthews CE, Moore SC, Arem H, Cook MB, Trabert B, Hakansson N, et al. Amount and intensity of leisure-time physical activity and lower cancer risk. J Clin Oncol 2020;38:686–98.

239. Patel AV, Friedenreich CM, Moore SC, Hayes SC, Silver JK, Campbell KL, et al. American College of Sports Medicine roundtable report on physical activity, sedentary behavior, and cancer prevention and control. Med Sci Sports Exerc 2019;51:2391–402.

REFERENCES

240. Moore SC, Lee IM, Weiderpass E, Campbell PT, Sampson JN, Kitahara CM, et al. Association of leisure-time physical activity with risk of 26 types of cancer in 1.44 million adults. JAMA Intern Med 2016;176:816–25.

241. World Cancer Research Fund/American Institute for Cancer Research. Diet and Cancer Report. Continuous Update Project. Expert Report. Diet, nutrition, physical activity and cancer: a global perspective. Available from: https://www.wcrf.org/diet-and-cancer/.

242. Luby-Secretan B, Scoccianti C, Loomis D, Grosse Y, Bianchini F, Straif K, et al. Body fatness and cancer - viewpoint of the IARC Working Group. N Engl J Med 2016;375:794–8.

243. World Cancer Research Fund/American Institute for Cancer Research. Continuous Update Project. Expert Report 2018. Body fatness and weight gain and the risk of cancer. Available from: dietandcancerreport.org.

244. Ogden CL, Fryar CD, Martin CB, Freedman DS, Carroll MD, Gu Q, et al. Trends in obesity prevalence by race and hispanic origin - 1999-2000 to 2017-2018. JAMA 2020;324:1208–10.

245. Kwak YE, McMillan R, McDonald EK 4th. Trends in overweight and obesity self-awareness among adults with overweight or obesity in the United States, 1999 to 2016. Ann Intern Med 2021;174:721–3.

246. Katzmarzyk PT, Martin CK, Newton RL Jr, Apolzan JW, Arnold CL, Davis TC, et al. Weight loss in underserved patients — a cluster-randomized trial. N Engl J Med 2020;383:909–18.

247. Centers for Disease Control and Prevention. COVID-19: people with certain medical conditions. [updated 2021 May 13; cited 2021 Jul 11]. Available from: https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html.

248. Xie W, Lundberg DJ, Collins JM, Johnston SS, Waggoner JR, Hsiao CW, et al. Association of weight loss between early adulthood and midlife with all-cause mortality risk in the US. JAMA Netw Open 2020;3:e2013448.

249. Tao W, Santoni G, von Euler-Chelpin M, Ljung R, Lynge E, Pukkala E, et al. Cancer risk after bariatric surgery in a cohort study from the five Nordic countries. Obes Surg 2020;30:3761–7.

250. Schauer DP, Feigelson HS, Koebnick C, Caan B, Weinmann S, Leonard AC, et al. Bariatric surgery and the risk of cancer in a large multisite cohort. Ann Surg 2019;269:95–101.

251. DocWire News. Weight loss surgery cuts risk of pancreatic cancer for obese patients with type 2 diabetes. 2020 Oct 14. [cited 2021 Jul 10]. Available from; https://www.docwirenews.com/hematology-oncology/weight-loss-surgery-cuts-risk-of-pancreatic-cancer-for-obese-patients-with-type-2-diabetes/.

252. Rock CL, Thomson C, Gansler T, Gapstur SM, McCullough ML, Patel AV, et al. American Cancer Society guideline for diet and physical activity for cancer prevention. CA Cancer J Clin 2020;70:245–71.

253. U.S. Department of Agriculture and U.S. Department of Health and Human Services. Dietary guidelines for Americans: 2020-2025. 9th edition; December 2020; Available from: https://www.dietaryguidelines.gov/sites/default/files/2021-03/Dietary_Guidelines_for_Americans-2020-2025.pdf.

254. Zhang FF, Cudhea F, Shan Z, Michaud DS, Imamura F, Eom H, et al. Preventable cancer burden associated with poor diet in the United States. JNCI Cancer Spectr 2019;3:pkz034.

255. Wang DD, Li Y, Bhupathiraju SN, Rosner BA, Sun Q, Giovannucci EL, et al. Fruit and vegetable intake and mortality: results from 2 prospective cohort studies of US men and women and a meta-analysis of 26 cohort studies. Circulation 2021;143:1642–54.

256. Veettil SK, Tse YW, Loo YS, Playdon MC, Lai NM, Giovannucci EL, et al. Role of diet in colorectal cancer incidence umbrella review of Meta-analyses of prospective observational studies. JAMA Netw Open 2021;4:e2037341.

257. Gurjao C, Zhong R, Haruki K, Li YY, Spurr LF, Lee-Six H, et al. Discovery and features of an alkylating signature in colorectal cancer. Cancer Discov 2021 Jun 17 [Epub ahead of print].

258. Lange SJ, Moore LV, Harris DM, Merlo CL, Lee SH, Demissie Z, et al. Percentage of Adolescents Meeting Federal Fruit and Vegetable Intake Recommendations — Youth Risk Behavior Surveillance System, United States, 2017. MMWR Morb Mortal Wkly Rep 2021;70:69–74.

259. Good M, Braun AC, Taylor CA, Spees CK. US adults fall short of the dietary guidelines for cancer prevention regardless of BMI category. J Acad Nutr Diet 2021 Mar 30 [Epub ahead of print].

260. Myers CA, Mire EF, Katzmarzyk PT. Trends in adiposity and food insecurity among US adults. JAMA Netw Open 2020;3:e2012767.

261. U.S. Food & Drug Adminstration. What's new with the nutrition facts label. [updated 2020 Mar 11; cited 2021 Jul 10]. Available from: https://www.fda.gov/food/new-nutrition-facts-label/whats-new-nutrition-facts-label.

262. American Cancer Society. Cancer prevention & early detection: facts & figures 2021-2022. Atlanta: American Cancer Society: 2021.

263. Koyratty N, McCann SE, Millen AE, Nie J, Trevisan M, Freudenheim JL. Sugar-sweetened soda consumption and total and breast cancer mortality: The Western New York exposures and Breast Cancer (WEB) study. Cancer Epidemiol Biomarkers Prev 2021;30:945–52.

264. Hur J, Otegbeye E, Joh HK, Nimptsch K, Ng K, Ogino S, et al. Sugar-sweetened beverage intake in adulthood and adolescence and risk of early-onset colorectal cancer among women. Gut 2021 May 6 [Epub ahead of print].

265. Chazelas E, Srour B, Desmetz E, Kess-Guyot E, Julia C, Deschamps V, et al. Sugary drink consumption and risk of cancer: results from NutriNet-Santé prospective cohort. BMJ 2019;366:12408.

266. Rosinger A, Herrick K, Gahche J, Park S. Sugar-sweetened beverage consumption among U.S. youth, 2011-2014. NCHS Data Brief 2017;271:1–8.

267. Rosinger A, Herrick K, Gahche J, Park S. Sugar-sweetened beverage consumption among U.S. adults, 2011-2014. NCHS Data Brief 2017;270:1–8.

268. Joh HK, Lee DH, Hur J, Nimptsch K, Chang Y, Joung H, et al. Simple sugar and sugar-sweetened beverage intake during adolescence and risk of colorectal cancer precursors. Gastroenterology 2021;161:128–42.

269. Vercammen KA, Moran AJ, Soto MJ, Kennedy-Shaffer L, Bleich SN. Decreasing trends in heavy sugar-sweetened beverage consumption in the United States, 2003 to 2016. J Acad Nutr Diet 2020;120:1974–85.

270. Du M, Griecci CF, Kim DD, Cudhea F, Ruan M, Eom H, et al. Cost-effectiveness of a national sugar-sweetened beverage tax to reduce cancer burdens and disparities in the United States. JNCI Cancer Spectr 2021;4:pkaa073.

271. Du M, Griecci CF, Cudhea FF, Eom H, Kim DD, Wilde P, et al. Cost-effectiveness analysis of nutrition facts added-sugar labeling and obesity-associated cancer rates in the US. JAMA Netw Open 2021:4:e217501.

272. Gilchrist SC, Howard VJ, Akinyemiju T, Judd SE, Cushman M, Hooker SP, et al. Association of sedentary behavior with cancer mortality in middle-aged and older US adults. JAMA Oncol 2020;6:1210–7.

273. American Cancer Society. Cancer prevention & early detection facts & figures 2019-2020. Atlanta: American Cancer Society; 2019.

274. Stockwell S, Trott M, Tully M, Shin J, Barnett Y, Butler L, et al. Changes in physical activity and sedentary behaviours from before to during the COVID-19 pandemic lockdown: a systematic review. BMJ Open Sport Exerc Med 2021;7:e000960.

275. Katzmarzyk PT, Friedenreich C, Shiroma EJ, Lee IM. Physical inactivity and non-communicable disease burden in low-income, middle-income and high-income countries. Br J Sports Med 2021 Mar 29 [Epub ahead of print].

276. Bull FC, Al-Ansari SS, Biddle S, Borodulin K, Buman MP, Cardon G, et al. World Health Organization 2020 guidelines on physical activity and sedentary behaviour. Br J Sports Med 2020;54:1451–62.

277. Papadimitriou N, Markozannes G, Kanellopoulou A, Critselis E, Alhardan S, Karafousia V, et al. An umbrella review of the evidence associating diet and cancer risk at 11 anatomical sites. Nat Commun 2021;12:4579.

278. Hydes TJ, Burton R, Inskip H, Bellis MA, Sheron N. A comparison of gender-linked population cancer risks between alcohol and tobacco: how many cigarettes are there in a bottle of wine? BMC Public Heal 2019;19:316.

279. LoConte NK, Brewster AM, Kaur JS, Merrill JK, Alberg AJ. Alcohol and cancer: a statement of the American Society of Clinical Oncology. J Clin Oncol 2018;36:83–93.

280. White AJ, DeRoo LA, Weinberg CR, Sandler DP. Lifetime alcohol intake, binge drinking behaviors, and breast cancer risk. Am J Epidemiol 2017;186:541–9.

281. Xi B, Veeranki SP, Zhao M, Ma C, Yan Y, Mi J. Relationship of alcohol consumption to all-cause, cardiovascular, and cancer-related mortality in U.S. adults. J Am Coll Cardiol 2017;70:913–22.

282. Goding Sauer A, Fedewa SA, Bandi P, Miniham AK, Stoklosa M, Drope J, et al. Proportion of cancer cases and deaths attributable to alcohol consumption by US state, 2013-2016. Cancer Epidemiol 2021;71:101893.

283. Han BH, Moore AA, Ferris R, Palamar JJ. Binge drinking among older adults in the United States, 2015 to 2017. J Am Geriatr Soc 2019;67:2139–44.

284. Kanny D, Naimi TS, Liu Y, Brewer RD. Trends in total binge drinks per adult who reported binge drinking — United States, 2011–2017. MMWR Morb Mortal Wkly Rep 2020;69:30–4.

285. National Cancer Institute. Cancer Trends Progress Report. Alcohol consumption. [updated 2021 Jul; cited 2021 Jul 10]. Available from: https://progressreport.cancer.gov/prevention/alcohol.

286. Spencer MR, Curtin SC, Hedegaard H. Rates of alcohol-induced deaths among adults aged 25 and over in urban and rural areas: United States, 2000-2018. NCHS Data Brief 2020;383:1–8.

287. Pollard MS, Tucker JS, Green HD. Changes in adult alcohol use and consequences during the COVID-19 pandemic in the US. JAMA Netw Open 2020;3:e2022942.

288. McKnight-Eily LR, Okoro CA, Turay K, Acero C, Hungerford D. Screening for alcohol use and brief counseling of adults — 13 states and the District of Columbia, 2017. MMWR Morb Mortal Wkly Rep 2020;69:265–70.

289. Boersma P, Villarroel MA, Vahratian A. Heavy drinking among U.S. adults, 2018. NCHS Data Brief 2020;374:1–8.

290. GBD 2016 Alcohol and Drug Use Colaborators. The global burden of disease attributable to alcohol and drug use in 195 countries and territories, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet Psychiatry. 2018;5:987–1012.

291. Rumgay H, Shield K, Charvat H, Ferrari P, Sornpaisarn B, Obot I, et al. Global burden of cancer in 2020 attributable to alcohol consumption: a population-based study. Lancet Oncol 2021;22:1071–80.

292. Hobin E, Weerasinghe A, Vallance K, Hammond D, McGavock J, Greenfield TK, et al. Testing alcohol labels as a tool to communicate cancer risk to drinkers: a real-world quasi-experimental study. J Stud Alcohol Drugs 2020;81:249–61.

293. U.S. Department of the Treasury. Alcohol and Tobacco Tax and Trade Bureau. Available from: https://www.ttb.gov/.

294. Islami F, Sauer AG, Miller KD, Fedewa SA Minihan AK, Geller AC, et al. Cutaneous melanomas attributable to ultraviolet radiation exposure by state. Int J Cancer 2020;147:1385–90.

295. Dennis LK, Vanbeek MJ, Beane Freeman LE, Smith B, Dawson DV, Coughlin JA. Sunburns and risk of cutaneous melanoma: does age matter? A comprehensive meta-analysis. Ann Epidemiol 2008;18:61–27.

296. Welch HG, Mazer BL, Adamson AS. The rapid rise in cutaneous melanoma diagnoses. N Engl J Med 2021;384:72–9.

297. American Academy of Dermatology Association. New American Academy of Dermatology survey finds one-third of Americans fail basic quiz on skin cancer and sun exposure. 2021 Apr 27. Available from: https://www.aad.org/news/aad-survey-finds-americans-fail-skin-cancer-quiz.

298. Stapleton JL, Hrywna M, Coups EJ, Delnevo C, Heckman CJ, Xu B. Prevalence and location of indoor tanning among high school students in New Jersey 5 years after the enactment of youth access restrictions. JAMA Dermatol 2020;156:1223–7.

299. Eskander A, Marqueen KE, Edwards HA, Joshua AM, Petrella TM, de Almeida JR, et al. To ban or not to ban tanning bed use for minors: A cost-effectiveness analysis from multiple US perspectives for invasive melanoma. Cancer 2021;127:2333–41.

300. de Martel C, Georges D, Bray F, Ferlay J, Clofford GM. Global burden of cancer attributable to infections in 2018: a worldwide incidence analysis. Lancet Glob Heal 2020;8:e180–90.

301. Hong CY, Sinn DH, Kang D, Paik SW, Guallar E, Cho J, et al. Incidence of extrahepatic cancers among individuals with chronic hepatitis B or C virus infection: a nationwide cohort study. J Viral Hepat 2020;27:896–903.

302. Ryerson AB, Schillie S, Barker LK, Kupronis BA, Wester C. Vital signs: newly reported acute and chronic hepatitis C cases —United States, 2009–2018. MMWR Morb Mortal Wkly Rep 2020;69:399–404.

303. US Preventive Services Task Force, Owens DK, Davidson KW, Krist AH, Barry MJ, Cabana M, et al. Screening for hepatitis C virus infection in adolescents and adults: US Preventive Services Task Force recommendation statement. JAMA 2020;323:970–5.

304. Schillie S, Wester C, Osborne M, Wesolowski L, Ryerson AB. CDC recommendations for hepatitis C screening among adults — United States, 2020. MMWR Recomm Rep 2020;69:1–17.

REFERENCES

305. Kaufman HW, Bull-Otterson L, Meyer WA 3rd, Huang X, Doshani M, Thompson WM, et al. Decreases in hepatitis C testing and treatment during the COVID-19 pandemic. Am J Prev Med 2021 May 10 [Eppub ahead of print].

306. U.S. Department of Health and Human Services. 2020. Viral hepatitis national strategic plan for the United States: a roadmap to elimination (2021–2025). Washington, DC. Available from: https://www.hhs.gov/sites/default/files/Viral-Hepatitis-National-Strategic-Plan-2021-2025.pdf.

307. Centers for Disease Control and Prevention. HPV and cancer: cancers associated with human papillomavirus (HPV). [updated 2020 Sep 3; cited 2021 Jul 11]. Available from: https://www.cdc.gov/cancer/hpv/basic_info/cancers.htm.

308. Rosenblum HG, Lewis RM, Gargano JW, Querec TD, Unger ER, Markowitz LE. Declines in prevalence of human papillomavirus vaccine-type infection among females after introduction of vaccine — United States, 2003–2018. MMWR Morb Mortal Wkly Rep 2021;70:415–20.

309. Lei J, Ploner A, Elfström KM, Wang J, Roth A, Fang F, et al. HPV vaccination and the risk of invasive cervical cancer. 2020;383:1340–8.

310. Mix JM, van Dyne EA, Saraiya M, Hallowell BD, Thomas CC. Assessing impact of HPV vaccination on cervical cancer incidence among women aged 15–29 years in the United States, 1999–2017: an ecologic study. Cancer Epidemiol Biomarkers Prev 2021;30:30–7.

311. Pingali C. National, Regional, State, and Selected Local Area Vaccination Coverage Among Adolescents Aged 13–17 Years — United States, 2020. MMWR Morb Mortal Wkly Rep. 2021;70:1183-1190.

312. Williams EA, Newberg J, Williams KJ, Montesion M, Alexander BM, Lin DL, et al. Prevalence of high-risk nonvaccine human papillomavirus types in advanced squamous cell carcinoma among individuals of African vs non-African ancestry. JAMA Netw Open 2021;4:e216481.

313. Szilagyi PG, Humiston SG, Stephens-Shields AJ, Localio R, Breck A, Kelly MK, et al. Effect of training pediatric clinicians in human papillomavirus communication strategies on human papillomavirus vaccination rates: a cluster randomized clinical trial. JAMA Pediatr 2021 May 24 [Epub ahead of print].

314. Sonawane K, Zhu Y, Lin YY, Damgacioglu H, Lin Y, Montealegre JR, et al. HPV vaccine recommendations and parental intent. Pediatrics 2021;147:e2020026286.

315. Murthy VH. Confronting health misinformation: the U.S. Surgeon General's advisory on building a healthy information environment. Available from: https://www.hhs.gov/sites/default/files/surgeon-general-misinformation-advisory.pdf.

316. Ambrosone CB, Higgins MJ. Relationships between breast feeding and breast cancer subtypes: lessons learned from studies in humans and in mice. Cancer Res 2020;80:4871–7.

317. Lord SJ, Bernstein L, Johnson KA, Malone KE, McDonald JA, Marchbanks PA, et al. Breast cancer risk and hormone receptor status in older women by parity, age of first birth, and breastfeeding: a case-control study. Cancer Epidemiol Biomarkers Prev 2008;17:1723–30.

318. World Cancer Research Fund/American Institute for Cancer Research. Continuous Update Project. Expert Report 2018. Lactation and the risk of cancer. Available from: https://www.wcrf.org/wp-content/uploads/2021/02/Lactation.pdf.

319. Palmer JR, Viscidi E, Troester MA, Hong CC, Schedin P, Bethea TN, et al. Parity, lactation, and breast cancer subtypes in African American women: results from the AMBER Consortium. J Natl Cancer Inst 2014;106:dju237.

320. Islami F, Liu Y, Jemal A, Zhou J, Weiderpass E, Colditz G, et al. Breastfeeding and breast cancer risk by receptor status - a systematic review and meta-analysis. Ann Oncol 2015;26:2398–407.

321. Moorman PG, Alberg AJ, Bandera EV, Barnholtz-Sloan J, Bondy M, Cote ML, et al. Reproductive factors and ovarian cancer risk in African-American women. Ann Epidemiol 2016;26:654–62.

322. Babic A, Sasamoto N, Rosner BA, Tworoger SS, Jordan SJ, Risch HA, et al. Association between breastfeeding and ovarian cancer risk. JAMA Oncol 2020;6:e200421.

323. Hoyt-Austin A, Dove MS, Abrahão R, Kair LR, Schwarz EB. Awareness that breastfeeding reduces breast cancer risk: 2015-2017 National Survey of Family Growth. Obstet Gynecol 2020;136:1154–6.

324. Chiang KV., Li R, Anstey EH, Perrine CG. Racial and ethnic disparities in breastfeeding initiation —United States, 2019. MMWR Morb Mortal Wkly Rep 2021;70:769–74.

325. Beauregard JL, Hamner HC, Chen J, Avila-Rodriguez W, Elam-Evans LD, Perrine CG. Racial disparities in breastfeeding initiation and duration among U.S. infants born in 2015. MMWR Morb Mortal Wkly Rep 2019;68:745–8.

326. Chlebowski RT, Anderson GL, Aragaki AK, Manson JE, Stefanick ML, Pan K, et al. Association of menopausal hormone therapy with breast cancer incidence and mortality during long-term follow-up of the Women's Health Initiative Randomized Clinical Trials. JAMA 2020;324:369–80.

327. Chlebowski RT, Anderson G, Pettinger M, Lane D, Langer RD, Gilligan MA, et al. Estrogen plus progestin and breast cancer detection by means of mammography and breast biopsy. Arch Intern Med 2008;168:370–7.

328. Collaborative Group on Hormonal Factors in Breast Cancer. Type and timing of menopausal hormone therapy and breast cancer risk: individual participant meta-analysis of the worldwide epidemiological evidence. Lancet 2019;394:1159–68.

329. Chlebowski RT, Kuller LH, Prentice RL, Stefanick ML, Manson JE, Gass M, et al. Breast cancer after use of estrogen plus progestin in postmenopausal women. N Engl J Med 2009;360:573–87.

330. Rosenberg L, Bethea TN, Viscidi E, Hong CC, Troester MA, Bandera EV, et al. Postmenopausal female hormone use and estrogen receptor–positive and –negative breast cancer in African American women. J Natl Cancer Inst 2016;108:361.

331. Ellingjord-Dale M, Vos L, Tretli S, Hofvind S, Dos-Santos-Silva I, Ursin G. Parity hormones and breast cancer subtypes - results from a large nested case-control study in a national screening program. Breast Cancer Res 2017;19:10.

332. Vinogradova Y, Coupland C, Hippisley-Cox J. Use of hormone replacement therapy and risk of breast cancer: nested case-control studies using the QResearch and CPRD databases. BMJ 2020;371:m3873.

333. National Cancer Institute, NIH, DHHS. Cancer trends progress report. Bethesda, MD, 2021 Jul. Available from: https://progressreport.cancer.gov/.

334. U.S. Department of Health and Human Services. 14th report on carcinogens. [updated 2016 Nov 3; cited 2021 Jul 10]. Available from: https://ntp.niehs.nih.gov/whatwestudy/assessments/cancer/roc/index.html.

335. Li N, Zhai Z, Zheng Y, Lin S, Deng Y, Xiang G, et al. Association of 13 occupational carcinogens in patients with cancer, individually and collectively, 1990-2017. JAMA Netw Open 2021;4:e2037530.

336. Loomis D, Grosse Y, Lauby-Secretan B, El Ghissassi F, Bouvard V, Benbrahim-Tallaa L, et al. The carcinogenicity of outdoor air pollution. Lancet Oncol 2013;14:1262–3.

337. Baurick T, Younes L, Meiners J. Welcome to "cancer alley," where toxic air is about to get worse. ProPublica 2019 Oct 30. Available from:. https://www.propublica.org/article/welcome-to-cancer-alley-where-toxic-air-is-about-to-get-worse.

338. Serrano MJ, Garrido-Navas MC, Diaz Mochon JJ, Cristofanilli M, Gil-Bazo I, Pauwels P, et al. Precision prevention and cancer interception: the new challenges of liquid biopsy. Cancer Discov 2020;10:1635–44.

339. Klein CA. Cancer progression and the invisible phase of metastatic colonization. Nat Rev Cancer 2020;20:681–94.

340. Eden RE, Coviello JM. Chronic myelogenous leukemia. In: StatPearls. Treasure Island (FL): StatPearls Publishing; 2021.

341. De Rubis G, Rajeev Krishnan S, Bebawy M. Liquid biopsies in cancer diagnosis, monitoring, and prognosis. Trends Pharmacol Sci 2019;40:172–86.

342. Levy SE, Myers RM. Advancements in next-generation sequencing. Annu Rev Genomics Hum Genet 2016;17:95–115.

343. Klein EA, Richards D, Cohn A, Tummala M, Lapham R, Cosgrove D, et al. Clinical validation of a targeted methylation-based multi-cancer early detection test using an independent validation set. Ann Oncol 2021;32:1167–77.

344. Liu MC, Oxnard GR, Klein EA, Swanton C, Seiden MV, CCGA Consortium. Sensitive and specific multi-cancer detection and localization using methylation signatures in cell-free DNA. Ann Oncol 2020;31:745–59.

345. Liu MC. Transforming the landscape of early cancer detection using blood tests—commentary on current methodologies and future prospects. Br J Cancer 2021 124:1475–77.

346. Hubbell E, Clarke CA, Aravanis AM, Berg CD. Modeled reductions in late-stage cancer with a multi-cancer early detection test. Cancer Epidemiol Biomarkers Prev 2021;30:460–8.

347. Hathaway C, Paetsch P, Li Y, Wu J, Asgarian S, Parker A, et al. Association of breast cancer screening behaviors with stage at breast cancer diagnosis and potential for additive multi-cancer detection via liquid biopsy screening: a claims-based study. Front Oncol 2021;11:688455.

348. Keller L, Belloum Y, Wikman H, Pantel K. Clinical relevance of blood-based ctDNA analysis: mutation detection and beyond. Br J Cancer 2021;124:345–58.

349. Svoboda E. Artificial intelligence is improving the detection of lung cancer. Nature 2020;587:S20–2.

350. Van Booven DJ, Kuchakulla M, Pai R, Frech FS, Ramasahayam R, Reddy P, et al. A systematic review of artificial intelligence in prostate cancer. Res Reports Urol 2021;13:31–9.

351. Pacilè S, Lopez J, Chone P, Bertinotti T, Grouin JM, Fillard P. Improving breast cancer detection accuracy of mammography with the concurrent use of an artificial intelligence tool. Radiol Artif Intell 2020;2:e190208.

352. The Food and Drug Administration. FDA News Release. FDA authorizes marketing of first device that uses artificial intelligence to help detect potential signs of colon cancer. 2021 Apr 9. Available from: https://www.fda.gov/news-events/press-announcements/fda-authorizes-marketing-first-device-uses-artificial-intelligence-help-detect-potential-signs-colon.

353. Dias R, Torkamani A. Artificial intelligence in clinical and genomic diagnostics. Genome Med 2019;11:70.

354. Callaway E. "It will change everything": DeepMind's AI makes gigantic leap in solving protein structures. Nature 2020;588:203–4.

355. Paul D, Sanap G, Shenoy S, Kalyane D, Kalia K, Tekade RK. Artificial intelligence in drug discovery and development. Drug Discov Today 2021;26:80–93.

356. Savage N. How AI is improving cancer diagnostics. Nature 2020;579:S14–6.

357. Mittra I, Mishra GA, DIkshit RP, Gupta S, Kulkarni VY, Shaikh HKA, et al. Effect of screening by clinical breast examination on breast cancer incidence and mortality after 20 years: prospective, cluster randomised controlled trial in Mumbai. BMJ 2021;372:n256.

358. National Lung Screening Trial Researh Team, Aberle DR, Adams AM, Berg CD, Black WC, Clapp JD, et al. Reduced l;ung-cancer mortality with low-dose computed tomographic screening. N Engl J Med 2011;365:395–409.

359. de Koning HJ, van der Aalst CM, de Jong PA, Scholten ET, Nackaerts K, Heuvelmans MA, et al. Reduced lung-cancer mortality with volume CT screening in a randomized trial. N Engl J Med 2020;382:503–13.

360. US Preventive Services Task Force, Krist AH, Davidson KW, Mangione CM, Barry MJ, Cabana M, et al. Screening for lung cancer: US Preventive Services Task Force recommendation statement. JAMA 2021;325:962–70.

361. Aldrich MC, Mercaldo SF, Sandler KL, Blot WJ, Grogan EL, Blume JD. Evaluation of USPSTF lung cancer screening guidelines among African American adult smokers. JAMA Oncol 2019;5:1318–24.

362. Duffy SW, Vulkan D, Cuckle H, Parmar D, Sheikh S, Smith RA, et al. Effect of mammographic screening from age 40 years on breast cancer mortality (UK Age trial): final results of a randomised, controlled trial. Lancet Oncol 2020;21:1165–72.

363. Nazari SS, Mukherjee P. An overview of mammographic density and its association with breast cancer. Breast Cancer 2018;25:259–67.

364. Brown GR, Simon M, Wentling C, Spencer DM, Parker AN, Rogers CA. A review of inherited cancer susceptibility syndromes. JAAPA 2020;33:10–6.

365. Kassem N, Stout LA, Hunter C, Schneider B, Radovich M. Precision prevention: the current state and future of genomically guided cancer prevention. JCO Precis Oncol. 2020;4:96–108.

366. Yedjou CG, Sims JN, Miele L, Noubissi F, Lowe L, Fonseca DD, et al. Health and racial disparity in breast cancer. Ad Exp Med Biol 2019;1152:31–49.

367. Rebner M, Pai VR. Breast cancer screening recommendations: African American women are at a disadvantage. J Breast Imaging 2020;2:416–21.

368. Benavidez GA, Zgodic A, Zahnd WE, Eberth JM. Disparities in meeting USPSTF breast, cervical, and colorectal cancer screening guidelines among women in the United States. Prev Chronic Dis 2021;18:E37.

REFERENCES

369. Washington SL 3rd, Jeong CW, Lonergan PE, Herlemann A, Gomez SL, Carroll PR, et al. Regional variation in active surveillance for low-risk prostate cancer in the US. JAMA Netw Open 2020;3:e2031349.

370. Zgodic A, Zahnd WE, Advani S, Eberth JM. Low-dose CT lung cancer screening uptake: a rural–urban comparison. J Rural Heal 2021 Mar 18 [Epub ahead of print].

371. United States Census Bureau. Poverty thresholds. [updated 2021 Feb 2; cited 2021 Apr 27]. Available from: https://www.census.gov/data/tables/time-series/demo/income-poverty/historical-poverty-thresholds.html.

372. Bakouny Z, Paciotti M, Schmidt AL, Lipsitz SR, Choueiri TK, Trinh QD. Cancer screening tests and cancer diagnoses during the COVID-19 pandemic. JAMA Oncol 2021;7:458–60.

373. Epic Health Research Network. Delayed cancer screenings. 2020 May 4; [updated 2020 Jul 17]. Available from: https://ehrn.org/articles/delays-in-preventive-cancer-screenings-during-covid-19-pandemic/.

374. Sabatino SA, Thompson TD, White MC, Shapiro JA, de Moor J, Doria-Rose VP, et al. Cancer screening test receipt — United States , 2018. MMWR Morb Mortal Wkl Rep 2021;70:29–35.

375. Moss JL, Roy S, Shen C, Cooper JD, Lennon RP, Lengerich EJ, et al. Geographic variation in overscreening for colorectal, cervical, and breast cancer among older adults. JAMA Netw Open. 2020;3:e2011645.

376. Wright JD, Chen L, Tergas AI, Melamed A, St Clair CM, Hou JY, et al. Overuse of cervical cancer screening tests among women with average risk in the United States from 2013 to 2014. JAMA Netw Open 2021;4:e218373.

377. Huf SW, Asch DA, Volpp KG, Reitz C, Mehta SJ. Text messaging and opt-out mailed outreach in colorectal cancer screening: a randomized clinical trial. J Gen Intern Med 2021;36:1958–64.

378. Zhu X, Parks PD, Weiser E, Fischer K, Griffin JM, Limburg, et al. National survey of patient factors associated with colorectal cancer screening preferences. Cancer Prev Res 2021;14:603–14.

379. Sprague BL, Lowry KP, Miglioretti DL, Alsheik N, Bowles EJA, Tosteson ANA, et al. Changes in mammography utilization by women's characteristics during the first 5 months of the COVID-19 pandemic. J Natl Cancer Inst 2021 Mar 29 [Epub ahead of print].

380. Miller MJ, Xu L, Qin J, Hahn EE, Ngo-Metzger Q, Mittman B, et al. Impact of COVID-19 on cervical cancer screening rates among women aged 21-65 years in a large integrated health care system - Southern California, January 1-September 30, 2019, and January 1-September 30, 2020. MMWR Morb Mortal Wkly Rep 2021;70:109–13.

381. McBain RK, Cantor JH, Jena AB, Pera MF, Bravata DM, Whaley CM. Decline and rebound in routine cancer screening rates during the COVID-19 pandemic. J Gen Intern Med 2021;36:1829–31.

382. Preston MA, Ross L, Chukmaitov A, Smith SA, Odlum ML, Dahman B, et al. Health insurance coverage mandates: colorectal cancer screening in the post-ACA era. Cancer Prev Res 2021;14:123–30.

383. Westfall JM, Mold J, Fagnan L. Practice-based research - "blue highways" on the NIH roadmap. J Am Med Assoc 2007;297:403–6.

384. Li A, Bergan RC. Clinical trial design: past, present, and future in the context of big data and precision medicine. Cancer 2020;126:4838–46.

385. Van Norman GA. Update to drugs, devices, and the FDA: how recent legislative changes have impacted approval of new therapies. JACC Basic to Transl Sci 2020;5:831–9.

386. Park JJH, Hsu G, Siden EG, Thorlund K, Mills EJ. An overview of precision oncology basket and umbrella trials for clinicians. CA Cancer J Clin 2020;70:125–37.

387. NIH, National Cancer Institue. NCI-MATCH Precision Medicine Clinical Trial. [updated 2021 May 12; cited 2021 Aug 9]. Available from: https://www.cancer.gov/about-cancer/treatment/clinical-trials/nci-supported/nci-match.

388. U.S. Food & Drug Adminstration. Master protocols: efficient clinical trial design strategies to expedite development of oncology drugs and biologics guidance for industry, draft guidance for industry. 2018 Oct. Available from: https://www.fda.gov/media/120721/download.

389. Ajmera Y, Singhal S, Dwivedi SN, Dey AB. The changing perspective of clinical trial designs. Perspect Clin Res 2021;12:66–71.

390. Flaherty KT, Doroshow JH, Galbraith S, Ribas A, Kluetz PG, Pazdur R, et al. Rethinking cancer clinical trial conduct induced by COVID-19: an academic center, industry, government, and regulatory agency perspective. Cancer Discov 2021;11:1881–5.

391. Katib AA. Research ethics challenges during the COVID-19 pandemic: what should and what should not be done. J Ideas Heal 2020;3(Special 1):185–7.

392. Ajewole VB, Akindele O, Abajue U, Ndulue O, Marshall JJ, Mossi YT. Cancer disparities and Black American representation in clinical trials leading to the approval of oral chemotherapy drugs in the United States between 2009 and 2019. JCO Oncol Pract 2021;17:e623–8.

393. Lythgoe MP, Krell J, Savage P, Prasad V. Race reporting and diversity in US Food and Drug Administration (FDA) registration trials for prostate cancer; 2006–2020. Prostate Cancer Prostatic Dis 2021 Apr 15 [Epub ahead of print].

394. Gopishetty S, Kota V, Guddati AK. Age and race distribution in patients in phase III oncology clinical trials. Am J Transl Res 2020;12:5977–83.

395. Sullenger RD, Deal AM, Grilley Olson JE, Matson M, Swift C, Lux L, et al. Health insurance payer type and ethnicity are associated with cancer clinical trial enrollment among adolescents and young adults. J Adolesc Young Adult Oncol 2021 May 19 [Epub ahead of print].

396. Falzone L, Salomone S, Libra M. Evolution of cancer pharmacological treatments at the turn of the third millennium. Front Pharmacol 2018;9:1300.

397. Lawrence W. History of surgical oncology. In: Surgery: basic science and clinical evidence: 2nd Edition. New York: Springer-Verlag; 2008.

398. Gianfaldoni S, Gianfaldoni R, Wollina U, Lotti J, Tchernev G, Lotti T. An overview on radiotherapy: from its history to its current applications in dermatology. Open Access Maced J Med Sci 2017;5:521–5.

399. DeVita VT, Chu E. A history of cancer chemotherapy. Cancer Res 2008;68:8643–53.

400. Dobashi Y, Goto A, Kimura M, Nakano T. Molecularly targeted therapy: past, present and future. Chemother Open Access 2012;1:1000105

401. Zhang Y, Zhang Z. The history and advances in cancer immunotherapy: understanding the characteristics of tumor-infiltrating immune cells and their therapeutic implications. Cell Mol Immunol 2020;17:807–21.

REFERENCES

402. Annesi CA, Poulson M, Mak KS, Tapan U, Dechert TA, Litle VR, et al. The impact of residential racial segregation on non-small cell lung cancer treatment and outcomes. Ann Thorac Surg 2021 May 22 [Epub ahead of print].

403. Goldberg EM, Berger Y, Sood D, Kurnit KC, Kim JS, Lee NK, et al. Differences in sociodemographic disparities between patients undergoing surgery for advanced colorectal or ovarian cancer. Ann Surg Oncol 2021 May 6 [Epub ahead of print].

404. Bui A, Yang L, Myint A, May FP. Race, ethnicity, and socioeconomic status are associated with prolonged time to treatment after a diagnosis of colorectal cancer: a large population-based study. Gastroenterology 2021;160:1394–6.

405. Moyers JT, Patel A, Shih W, Nagaraj G. Association of sociodemographic factors with immunotherapy receipt for metastatic melanoma in the US. JAMA Netw Open 2020;3:e2015656.

406. Coughlin SS, Chen J, Cortes JE. Health care access and utilization among adult cancer survivors: results from the National Institutes of Health "All of Us" Research Program. Cancer Med 2021;10:3646–54.

407. Gajarawala SN, Pelkowski JN. Telehealth benefits and barriers. J Nurse Pract 2021;17:218–21.

408. Burbury K, Wong ZW, Yip D, Thomas H, Brooks P, Gilham L, et al. Telehealth in cancer care: during and beyond the COVID-19 pandemic. Intern Med J 2021;51:125–33.

409. Purdy AC, Smith BR, Hohmann SF, Nguyen NT. The impact of the novel coronavirus pandemic on gastrointestinal operative volume in the United States. Surg Endosc 2021 Apr 19 [Epub ahead of print].

410. Riera R, Bagattini ÂM, Pacheco RL, Pachito DV, Roitberg F, Ilbawi A. Delays and disruptions in cancer health care due to COVID-19 pandemic: systematic review. JCO Glob Oncol 2021;7:311–23.

411. American Society of Radiation Oncology. COVID-19 & radiation oncology: results of a national physician survey by the American Society for Radiation Oncology (ASTRO) 2020. Available from: https://www.astro.org/ASTRO/media/ASTRO/News%20and%20Publications/PDFs/ASTRO_COVID19Survey_2021.pdf.

412. Elkrief A, Kazandjian S, Bouganim N. Changes in lung cancer treatment as a result of the coronavirus disease 2019 pandemic. JAMA Oncol 2020;6:1805–6.

413. Perera SK, Jacob S, Wilson BE, Ferlay J, Bray F, Sullivan R, et al. Global demand for cancer surgery and an estimate of the optimal surgical and anaesthesia workforce between 2018 and 2040: a population-based modelling study. Lancet Oncol 2021;22:182–9.

414. Burotto M, Wilkerson J, Stein WD, Bates SE, Fojo T. Adjuvant and neoadjuvant cancer therapies: a historical review and a rational approach to understand outcomes. Semin Oncol 2019;46:83–99.

415. Carneiro BC, Da Cruz IAN, Ormond Filho AG, Silv IP, Guimaraes JB, Silva FD, et al. Osteoid osteoma: the great mimicker. Insights Imaging 2021;12:32.

416. Sharma KV, Yarmolenko PS, Celik H, Eranki A, Partanen A, Smitthimedhin A, et al. Comparison of noninvasive high-intensity focused ultrasound with radiofrequency ablation of osteoid osteoma. J Pediatr 2017;190:222–8.

417. Liang G, Fan W, Luo H, Zhu X. The emerging roles of artificial intelligence in cancer drug development and precision therapy. Biomed Pharmacother 2020;128:110255.

418. Mole DJ, Fallowfield JA, Sherif AE, Kendall T, Semple S, Kelly M, et al. Quantitative magnetic resonance imaging predicts individual future liver performance after liver resection for cancer. PLoS One 2020;15:e0238568.

419. Jin L, Tang Y, Wu Y, Coole JB, Tan MT, Zhao X, et al. Deep learning extended depth-of-field microscope for fast and slide-free histology. Proc Natl Acad Sci U S A 2020;117:33051–60.

420. Ramirez PT, Frumovitz M, Pareja R, Lopez A, Vieira M, Ribeiro R, et al. Minimally invasive versus abdominal radical hysterectomy for cervical cancer. N Engl J Med 2018;379:1895–904.

421. Lewicki PJ, Basourakos SP, Qiu Y, Hu JC, Sheyn D, Hijaz A, et al. Effect of a randomized, controlled trial on surgery for cervical cancer. N Engl J Med 2021;384:1669–71.

422. Bryant AK, Banegas MP, Martinez ME, Mell LK, Murphy JD. Trends in radiation therapy among cancer survivors in the United States, 2000-2030. Cancer Epidemiol Biomarkers Prev 2017;26:963–70.

423. El Naqa I. Prospective clinical deployment of machine learning in radiation oncology. Nat Rev Clin Oncol 2021 Jul 9 [Epub ahead of print].

424. Lawhn-Heath C, Flavell RR, Behr SC, Yohannan T, Greene KL, Feng F, et al. Single-center prospective evaluation of 68Ga-PSMA-11 PET in biochemical recurrence of prostate cancer. Am J Roentgenol 2019;213:266–74.

425. Hope TA, Aggarwal R, Chee B, Tao D, Greene KL, Cooperberg MR, et al. Impact of 68Ga-PSMA-11 PET on management in patients with biochemically recurrent prostate cancer. J Nucl Med 2017;58:195–61.

426. Fendler WP, Calais J, Eiber M, Flavell RR, Mishoe A, Feng FY, et al. Assessment of 68Ga-PSMA-11 PET accuracy in localizing recurrent prostate cancer: a prospective single-arm clinical trial. JAMA Oncology 2019;5:856–63.

427. Calais J, Ceci F, Eiber M, Hope TA, Hofman MS, Rischpler C, et al. 18F-fluciclovine PET-CT and 68Ga-PSMA-11 PET-CT in patients with early biochemical recurrence after prostatectomy: a prospective, single-centre, single-arm, comparative imaging trial. Lancet Oncol 2019;20:1286–94.

428. Calais J, Fendler WP, Eiber M, Gartmann J, Chu FI, Nickols NG, et al. Impact of 68 Ga-PSMA-11 PET/CT on the management of prostate cancer patients with biochemical recurrence. J Nucl Med 2018;59:434–41.

429. Oronsky B, Ma PC, Morgensztern D, Carter CA. Nothing but NET: a review of neuroendocrine tumors and carcinomas. Neoplasia 2017;19:991–1002.

430. Herrmann K, Schwaiger M, Lewis JS, Solomon SB, McNeil BJ, Baumann M, et al. Radiotheranostics: a roadmap for future development. Lancet Oncol 2020;21:e146–56.

431. Kantarjian H, Kadia T, DiNardo C, Daver N, Borthakur G, Jabbour E, et al. Acute myeloid leukemia: current progress and future directions. Blood Cancer J 2021;11:41.

432. Wei AH, Döhner H, Pocock C, Montesinos P, Afanasyev B, Dombret H, et al. Oral azacitidine maintenance therapy for acute myeloid leukemia in first remission. N Engl J Med 2020;383:2526–37.

433. Acute Myeloid Leukemia News. FDA approves oral chemotherapy onureg for newly diagnosed AML patients in remission. 2020 Sep 3. Available from: https://acutemyeloidleukemianews.com/2020/09/03/fda-approves-oral-chemotherapy-onureg-for-newly-diagnosed-aml-patients-in-remission/.

434. van de Donk N, Pawlyn C, Yong KL. Multiple myeloma. Lancet 2021;397:410–27.

435. Wickström M, Nygren P, Larsson R, Harmenber J, Lindberg J, Sjoberg P, et al. Melflufen - a peptidase-potentiated alkylating agent in clinical trials. Oncotarget 2017;8:66641–55.

REFERENCES

436. Richardson PG, Oriol A, Larocca A, Blade J, Cavo M, Rodriguez-Otero P, et al. Melflufen and dexamethasone in heavily pretreated relapsed and refractory multiple myeloma. J Clin Oncol 2021;39:757–67.

437. Uprety D, Adjei AA. KRAS: from undruggable to a druggable cancer target. Cancer Treat Rev 2020;89:102070.

438. Ghimessy A, Radeczky P, Laszlo V, Hegedus B, Renyi-Vamos F, Fillinger J, et al. Current therapy of KRAS-mutant lung cancer. Cancer Metastasis Rev 2020;39:1159–77.

439. Dogan S, Shen R, Ang DC, Johnson ML, D'Angelo SP, Paik PK, et al. Molecular epidemiology of EGFR and KRAS mutations in 3,026 lung adenocarcinomas: higher susceptibility of women to smoking-related KRAS-mutant cancers. Clin Cancer Res 2012;18:6169–77.

440. Skoulidis F, Li BT, Dy GK, Price TJ, Falchook GS, Wolf J, et al. Sotorasib for lung cancers with KRAS p.G12C mutation . N Engl J Med 2021;384:2371–81.

441. Remon J, Hendriks LEL, Cardona AF, Besse B. EGFR exon 20 insertions in advanced non-small cell lung cancer: a new history begins. Cancer Treat Rev 2020;90:102105.

442. Neijssen J, Cardoso RMF, Chevalier KM, Wiegman LM, Valerius T, Anderson GM, et al. Discovery of amivantamab (JNJ-61186372), a bispecific antibody targeting EGFR and MET. J Biol Chem 2021;296:100641.

443. Socinski MA, Pennell NA, Davies KD. MET Exon 14 skipping mutations in non–small-cell lung cancer: an overview of biology, clinical outcomes, and testing considerations. JCO Precis Oncol 2021;5:PO.20.00516.

444. Comoglio PM, Trusolino L, Boccaccio C. Known and novel roles of the MET oncogene in cancer: a coherent approach to targeted therapy. Nat Rev Cancer 2018;18:341–58.

445. Paik PK, Felip E, Veillon R, Sakai H, Cortot AB, Garassino MC, et al. Tepotinib in non–small-cell lung cancer with MET Exon 14 skipping mutations. N Engl J Med 2020;383:931–43.

446. Ding SJ, Wang R, Peng SL, Xiaoqing L, Zhong LH, Yang H, et al. Targeted therapies for RET-fusion cancer: dilemmas and breakthrough. Biomed Pharmacother 2020;132:110901.

447. Gainor JF, Curigliano G, Kim DW, Lee DH, Besse B, Baik CS, et al. Pralsetinib for RET fusion-positive non-small-cell lung cancer (ARROW): a multi-cohort, open-label, phase 1/2 study. Lancet Oncol 2021;22:959–69.

448. Kitahara CM, Sosa JA. The changing incidence of thyroid cancer. Nat Rev Endocrinol 2016;12:646–53.

449. Salvatore D, Santoro M, Schlumberger M. The importance of the RET gene in thyroid cancer and therapeutic implications. Nat Rev Endocrinol 2021;17:296–306.

450. Kim J, Bradford D, Larkins E, Pai-Scherf LH, Chatterjee S, Mishra-Kalyani PS, et al. FDA approval summary: pralsetinib for the treatment of lung and thyroid cancers with RET gene mutations or fusions. Clin Cancer Res 2021 May 27 [Epub ahead of print].

451. Wang J, Xing X, Li Q, Zhang G, Wang T, Pan H, et al. Targeting the FGFR signaling pathway in cholangiocarcinoma: promise or delusion? Ther Adv Med Oncol 2020;12:1758835920940948.

452. Casadei C, Dizman N, Schepisi G, Cursano MC, Basso U, Santini D, et al. Targeted therapies for advanced bladder cancer: new strategies with FGFR inhibitors. Ther Adv Med Oncol 2019;11:1758835919890285.

453. Makawita S, Abou-Alfa GK, Roychowdhury S, Sadeghi S, Borbath I, Goyal L, et al. Infigratinib in patients with advanced cholangiocarcinoma with FGFR2 gene fusions/translocations: the PROOF 301 trial. Futur Oncol 2020;16:2375–84.

454. Sengupta R, Honey K. AACR cancer progress report 2019: transforming lives through innovative cancer science. Clin Cancer Res 2019;25:5431.

455. Helsten T, Elkin S, Arthur E, Tomson BN, Carter J, Kurzrock R. The FGFR landscape in cancer: analysis of 4,853 tumors by next-generation sequencing. Clin Cancer Res 2016;22:259–67.

456. Folkman J. Tumor angiogenesis: therapeutic implications. N Engl J Med. 1971;285:1182–6.

457. Lugano R, Ramachandran M, Dimberg A. Tumor angiogenesis: causes, consequences, challenges and opportunities. Cell Mol Life Sci 2020;77:1745–70.

458. Escudier B, Worden F, Kudo M. Sorafenib: key lessons from over 10 years of experience. Expert Rev Anticancer Ther 2019;19:177–89.

459. Szarek M, Needle MN, Rini BI, Pal SK, McDermott DF, Atkins MB, et al. Q-TWiST analysis of tivozanib versus sorafenib in patients with advanced renal cell carcinoma in the TIVO-3 Study. Clin Genitourin Cancer 2021 Apr 3 [Epub ahead of print].

460. Khongorzul P, Ling CJ, Khan FU, Ihsan AU, Zhang J. Antibody-drug conjugates: a comprehensive review. Mol Cancer Res 2020;18:3–19.

461. Robak P, Drozdz I, Szemraj J, Robak T. Drug resistance in multiple myeloma. Cancer Treat Rev 2018;70:199–208.

462. Yu B, Jiang T, Liu D. BCMA-targeted immunotherapy for multiple myeloma. J Hematol Oncol 2020;13:125.

463. Lonial S, Lee HC, Badros A, Trudel S, Nooka AK, Chari A, et al. Belantamab mafodotin for relapsed or refractory multiple myeloma (DREAMM-2): a two-arm, randomised, open-label, phase 2 study. Lancet Oncol 2020;21:207–21.

464. Wang K, Wei G, Liu D. CD19: a biomarker for B cell development, lymphoma diagnosis and therapy. Exp Hematol Oncol 2012;1:36.

465. Xiros N, Economopoulos T, Valsami S, Rontogianni D, Fountzilas G, Raptis S. Rituximab in combination with vinorelbine/gemcitabine chemotherapy in patients with primary refractory or early relapsed T cell rich B cell lymphoma: a pilot study. Leuk Res 2003;27:1097–9.

466. Hamadani M, Radford J, Carlo-Stella C, Caimi PF, Reid E, O'Connor OA, et al. Final results of a phase 1 study of loncastuximab tesirine in relapsed/refractory B-cell non-Hodgkin lymphoma. Blood 2021;137:2634–45.

467. Sengupta R, Honey K. AACR cancer progress report 2020: turning science into lifesaving care. Clin Cancer Res 2020;26:5055.

468. Yan M, Schwaederle M, Arguello D, Millis SZ, Gatalica Z, Kurzrock R. HER2 expression status in diverse cancers: review of results from 37,992 patients. Cancer Metastasis Rev 2015;34:157–64.

469. Zhao D, Klempner SJ, Chao J. Progress and challenges in HER2-positive gastroesophageal adenocarcinoma. J Hematol Oncol 2019;12:50.

470. Shitara K, Bang YJ, Iwasa S, Sugimoto N, Ryu MH, Sakai D, et al. Trastuzumab deruxtecan in previously treated HER2-positive gastric cancer. N Engl J Med 2020;382:2419–30.

471. FDA-NIH Biomarker Working Group. BEST (Biomarkers, EndpointS, and other Tools) resource. Silver Spring (MD): Food and Drug Administration (US); Bethesda (MD): National Institutes of Health (US); 2016.

472. Tagawa ST, Balar AV., Petrylak DP, Kalebsty AR, Loriot Y, Flechon A, et al. TROPHY-U-01: a phase II open-label study of sacituzumab govitecan in patients with metastatic urothelial carcinoma progressing after platinum-based chemotherapy and checkpoint inhibitors. J Clin Oncol 2021;39:2474–85.

473. Armitage JO, Gascoyne RD, Lunning MA, Cavalli F. Non-Hodgkin lymphoma. Lancet 2017;390:298–310.

474. Bojarczuk K, Wienand K, Chapuy B. Molecular classification of large B-cell non-Hodgkin lymphoma. Cancer J 2020;26:357–61.

475. Nguyen PH, Niesen E, Hallek M. New roles for B cell receptor associated kinases: when the B cell is not the target. Leukemia 2019;33:576–87.

476. Fowler NH, Samaniego F, Jurczak W, Ghosh N, Derenzini E, Reeves JA, et al. Umbralisib, a dual PI3Kδ/CK1ε inhibitor in patients with relapsed or refractory indolent lymphoma. J Clin Oncol 2021;39:1609–18.

477. Mato AR, Ghosh N, Schuster SJ, Lamanna N, Pagel JM, Flinn IW, et al. Phase 2 study of the safety and efficacy of umbralisib in patients with CLL who are intolerant to BTK or PI3Kδ inhibitor therapy. Blood 2021;137:2817–26.

478. Balis FM, Thompson PA, Mosse YP, Blaney SM, Minard CG, Weigel BJ, et al. First-dose and steady-state pharmacokinetics of orally administered crizotinib in children with solid tumors: a report on ADVL0912 from the Children's Oncology Group Phase 1/Pilot Consortium. Cancer Chemother Pharmacol 2017;79:181–7.

479. Crawford ED, Heidenreich A, Lawrentschuk N, Tombal B, Pompeo ACL, Mendoza-Valdes A, et al. Androgen-targeted therapy in men with prostate cancer: evolving practice and future considerations. Prostate Cancer Prostatic Dis 2019;22:24–38.

480. Nakata D, Masaki T, Tanaka A, Yoshimatsu M, Akinaga Y, Asada M, et al. Suppression of the hypothalamic-pituitary-gonadal axis by TAK-385 (relugolix), a novel, investigational, orally active, small molecule gonadotropin-releasing hormone (GnRH) antagonist: studies in human GnRH receptor knock-in mice. Eur J Pharmacol 2014;723:167–74.

481. Shore ND, Saad F, Cookson MS, George DJ, Saltzstein DR, Tutrone R, et al. Oral relugolix for androgen-deprivation therapy in advanced prostate cancer. N Engl J Med 2020;382:2187–96.

482. Waldman AD, Fritz JM, Lenardo MJ. A guide to cancer immunotherapy: from T cell basic science to clinical practice. Nat Rev Immunol 2020;20:651–68.

483. Dobosz P, Dzieciątkowski T. The intriguing history of cancer immunotherapy. Front Immunol 2019;10:2965.

484. Galluzzi L, Chan TA, Kroemer G, Wolchok JD, López-Soto A. The hallmarks of successful anticancer immunotherapy. Sci Transl Med 2018;10:eaat7807.

485. Kubli SP, Berger T, Araujo D V., Siu LL, Mak TW. Beyond immune checkpoint blockade: emerging immunological strategies. Nat Rev Drug Discov 2021 Mar 8 [Epub ahead of print].

486. Keilson JM, Knochelmann HM, Paulos CM, Kudchadkar RR, Lowe MC. The evolving landscape of immunotherapy in solid tumors. J Surg Oncol 2021;123:798–806.

487. Liu S, Galat V, Galat Y, Lee YKA, Wainwright D, Wu J. NK cell-based cancer immunotherapy: from basic biology to clinical development. J Hematol Oncol 2021;14:7.

488. Miller JS, Lanier LL. Natural killer cells in cancer immunotherapy. Annu Rev Cancer Biol 2019;3:77–103.

489. Mujal AM, Delconte RB, Sun JC. Natural killer cells: from innate to adaptive features. Annu Rev Immunol 2021;39:417–47.

490. Tonn T, Schwabe D, Klingemann HG, Becker S, Esser R, Koehl U, et al. Treatment of patients with advanced cancer with the natural killer cell line NK-92. Cytotherapy 2013;15:1563–70.

491. Dolstra H, Roeven MWH, Spanholtz J, Hangalapura BN, Tordoir M, Maas F, et al. Successful transfer of umbilical cord blood CD34+ hematopoietic stem and progenitor-derived NK cells in older acute myeloid leukemia patients. Clin Cancer Res 2017;23:4107–18.

492. Arai S, Meagher R, Swearingen M, Myint H, Rich E, Martinson J, et al. Infusion of the allogeneic cell line NK-92 in patients with advanced renal cell cancer or melanoma: a phase I trial. Cytotherapy 2008;10:625–32.

493. Wu SY, Fu T, Jiang YZ, Shao ZM. Natural killer cells in cancer biology and therapy. Mol Cancer 2020;19:120.

494. Ljunggren HG, Kärre K. In search of the "missing self": MHC molecules and NK cell recognition. Immunol Today 1990;11:237–44.

495. Suck G, Odendahl M, Nowakowska P, Seidl C, Wels WS, Klingemann HG, et al. NK-92: an 'off-the-shelf therapeutic' for adoptive natural killer cell-based cancer immunotherapy. Cancer Immunol Immunother 2016;65:485–92.

496. Veluchamy JP, Kok N, van der Vliet HJ, Verheul HMW, de Gruijl TD, Spanholtz J. The rise of allogeneic natural killer cells as a platform for cancer immunotherapy: recent innovations and future developments. Front Immunol 2017;8:631.

497. Lupo KB, Matosevic S. Natural killer cells as allogeneic effectors in adoptive cancer immunotherapy. Cancers 2019;11:769.

498. Nham T, Poznanski SM, Fan IY, Vahedi F, Shenouda MM, Lee AJ, et al. Ex vivo-expanded natural killer cells derived from long-term cryopreserved cord blood are cytotoxic against primary breast cancer cells. J Immunother 2018;41:64–72.

499. Freund-Brown J, Chirino L, Kambayashi T. Strategies to enhance NK cell function for the treatment of tumors and infections. Crit Rev Immunol 2018;38:105–31.

500. Mantesso S, Geerts D, Spanholtz J, Kučerová L. Genetic engineering of natural killer cells for enhanced antitumor function. Front Immunol 2020;11:607131.

501. Sharma P, Siddiqui BA, Anandhan S, Yadav SS, Subudhi SK, Gao J, et al. The next decade of immune checkpoint therapy. Cancer Discov 2021;11:838–57.

502. Makker V, Green AK, Wenham RM, Mutch D, Davidson B, Miller DS. New therapies for advanced, recurrent, and metastatic endometrial cancers. Gynecol Oncol Res Pract 2017;4:19.

503. Bonneville R, Krook MA, Kautto EA, Miya J, Wing MR, Chen HZ, et al. Landscape of microsatellite instability across 39 cancer types. JCO Precis Oncol 2017;;2017:PO.17.00073.

504. Oaknin A, Tinker A V., Gilbert L, Samouelian V, Mathews C, Brown J, et al. Clinical activity and safety of the anti-programmed death 1 monoclonal antibody dostarlimab for patients with recurrent or advanced mismatch repair-deficient endometrial cancer: a nonrandomized phase 1 clinical trial. JAMA Oncol 2020;6:1766–72.

505. Porpodis K, Zarogoulidis P, Boutsikou E, Papaioannou A, Machairiotis N, Tsakiridis K, et al. Malignant pleural mesothelioma: current and future perspectives. J Thorac Dis 2013;5(Suppl 4):S397–406.

REFERENCES

506. Baas P, Scherpereel A, Nowak AK, Fujimoto N, Peters S, Tsao AS, et al. First-line nivolumab plus ipilimumab in unresectable malignant pleural mesothelioma (CheckMate 743): a multicentre, randomised, open-label, phase 3 trial. Lancet 2021;397:375–86.

507. Stratigos AJ, Sekulic A, Peris K, Bechter O, Prey S, Kaatz M, et al. Cemiplimab in locally advanced basal cell carcinoma after hedgehog inhibitor therapy: an open-label, multi-centre, single-arm, phase 2 trial. Lancet Oncol 2021;22:848–57.

508. Sezer A, Kilickap S, Gümüş M, Bondarenko I, Ozguroglu M, Gogishvili M, et al. Cemiplimab monotherapy for first-line treatment of advanced non-small-cell lung cancer with PD-L1 of at least 50%: a multicentre, open-label, global, phase 3, randomised, controlled trial. Lancet 2021;397:592–604.

509. Kelly RJ, Ajani JA, Kuzdzal J, Zander T, Van Cutsem E, Piessen G, et al. Adjuvant nivolumab in resected esophageal or gastroesophageal junction cancer. N Engl J Med 2021;384:1191–203.

510. Cortes J, Cescon DW, Rugo HS, Nowecki Z, Im SA, Yusof MM, et al. Pembrolizumab plus chemotherapy versus placebo plus chemotherapy for previously untreated locally recurrent inoperable or metastatic triple-negative breast cancer (KEYNOTE-355): a randomised, placebo-controlled, double-blind, phase 3 clinical trial. Lancet 2020;396:1817–28.

511. Patrinely JR, Johnson R, Lawless AR, Bhave P, Sawyers A, Dimitrova M, et al. Chronic immune-related adverse events following adjuvant anti-PD-1 therapy for high-risk resected melanoma. JAMA Oncol 2021;7:744–8.

512. Rohaan MW, Wilgenhof S, Haanen JBAG. Adoptive cellular therapies: the current landscape. Virchows Arch 2019;474:449–61.

513. Depil S, Duchateau P, Grupp SA, Mufti G, Poirot L. 'Off-the-shelf' allogeneic CAR T cells: development and challenges. Nat Rev Drug Discov 2020;19:185–99.

514. Perez C, Gruber I, Arber C. Off-the-shelf allogeneic T cell therapies for cancer: opportunities and challenges using naturally occurring "universal" donor T cells. Front Immunol 2020;11:583716.

515. Munshi NC, Anderson LD, Shah N, Madduri D, Berdeja J, Lonial S, et al. Idecabtagene vicleucel in relapsed and refractory multiple myeloma. N Engl J Med 2021;384:705–16.

516. Abramson JS, Palomba ML, Gordon LI, Lunning MA, Wang M, Arnason J, et al. Lisocabtagene maraleucel for patients with relapsed or refractory large B-cell lymphomas (TRANSCEND NHL 001): a multicentre seamless design study. Lancet 2020;396:839–52.

517. Qin H, Ramakrishna S, Nguyen S, Fountaine TJ, Ponduri A, Stetler-Stevenson M, et al. Preclinical development of bivalent chimeric antigen receptors targeting both CD19 and CD22. Mol Ther Oncolytics 2018;11:127–37.

518. Nordstrom JL, Gorlatov S, Zhang W, Yang Y, Huang L, Burke S, et al. Anti-tumor activity and toxicokinetics analysis of MGAH22, an anti-HER2 monoclonal antibody with enhanced Fcγ receptor binding properties. Breast Cancer Res 2011;13:R123.

519. Rugo HS, Im SA, Cardoso F, Cortes J, Curigliano G, Musolino A, et al. Efficacy of margetuximab vs trastuzumab in patients with pretreated ERBB2-positive advanced breast cancer: a phase 3 randomized clinical trial. JAMA Oncol 2021;7:573–84.

520. Mitsogianni M, Trontzas IP, Gomatou G, Ioannou S, Syrigos NK, Kotteas EA. The changing treatment of metastatic her2-positive breast cancer. Oncol Lett 2021;21:287.

521. Van Arendonk K, Chung D. Neuroblastoma: tumor biology and its implications for staging and treatment. Children 2019;6:12.

522. Terzic T, Cordeau M, Herblot S, Teira P, Cournoyer S, Beaunoyer M, et al. Expression of disialoganglioside (GD2) in neuroblastic tumors: a prognostic value for patients treated with anti-GD2 immunotherapy. Pediatr Dev Pathol 2018;21:355–62.

523. National Coalition for Cancer Surviorship. Defining cancer survivorship. 2014 Jul 24. Available from: https://canceradvocacy.org/defining-cancer-survivorship/.

524. Shin J, Shin DW, Lee J, Hwang JH, Lee JE, Cho B, et al. Fear of cancer recurrence in stomach cancer survivors: exploring socio-demographic, physical, psychological and quality of life-related factors. Research Square. Available from: https://www.researchsquare.com/article/rs-378423/v1.

525. Biddle S. The psychological impact of active surveillance in men with prostate cancer: Implications for nursing care. Br J Nurs 2021;30:S30-S37.

526. Hutterer M, Oberndorfer S. Cognitive impairment in cancer patients and survivors—clinical presentation, pathophysiology, diagnosis and management. Mag Eur Med Oncol 2021;14:10.1007.

527. Mazariego CG, Laidsaar-Powell R, Smith DP, Juraskova I. Avoiding the 'survivorship abyss': qualitative insights from 15-year prostate cancer survivors. Psychooncology 2021 May 26 [Epub ahead of print].

528. Esselen KMK, Gompers A, Hacker MR, Bouberhan S, Shea M, Summerlin SS, et al. Evaluating meaningful levels of financial toxicity in gynecologic cancers. Int J Gynecol Cancer 2021;31:801-6.

529. Arastu A, Patel A, Mohile SG, Ciminelli J, Kaushik, R, Wells M, et al. Assessment of financial toxicity among older adults with advanced cancer. JAMA Netw Open 2020;3:e2025810.

530. Meernik C, Sandler DP, Peipins LA, Hodgson ME, Blinder VS, Wheeler SB, et al. Breast cancer–related employment disruption and financial hardship in the Sister Study. JNCI Cancer Spectr 2021;5:pkab024.

531. Gogate A, Wheeler SB, Reeder-Hayes KE, Ekwueme DU, Fairley TL, Drier S, et al. Projecting the prevalence and costs of metastatic breast cancer from 2015 through 2030. JNCI Cancer Spectr 2021;5:pkab063.

532. Erdmann F, Frederiksen LE, Bonaventure A, Mader L, Hasle H, Robison LL, et al. Childhood cancer: survival, treatment modalities, late effects and improvements over time. Cancer Epidemiol 2021;71(Pt B):101733.

533. Ghazal LV, Merriman J, Santacroce SJ, Dickson VV. Survivors' dilemma: young adult cancer survivors' perspectives of work-related goals. Workplace Health Saf 2021 May 27 [Epub ahead of print].

534. Chao C, Bhatia S, Xu L, Cannavale KL, Wong FL, Huang PYS, et al. Chronic comorbidities among survivors of adolescent and young adult cancer. J Clin Oncol 2020;38:3161–74.

535. Meernik C, Kirchhoff AC, Anderson C, Edwards TP, Deal AM, Baggett CD, et al. Material and psychological financial hardship related to employment disruption among female adolescent and young adult cancer survivors. Cancer 2020;127:137–48.

536. Children's Oncology Group. Long-term follow-up guidelines for survivors of childhood, adolescent, and young adult cancers. Version 5.0 - October 2018. [cited 2021 Jul 10]. Available from: www.survivorshipguidelines.org.

537. Advani P, Advani S, Nayak P, VonVille HM, Diamond P, Burnett J, et al. Racial/ethnic disparities in use of surveillance mammogram among breast cancer survivors: a systematic review. J Cancer Surviv 2021 May 13 [Epub ahead of print].

538. Berger MH, Lin HW, Bhattacharyya N. A national evaluation of food insecurity in a head and neck cancer population. Laryngoscope 2021;131:E1539–42.

539. Scott LC, Yang Q, Dowling NF, Richardson LC. Predicted heart age among cancer survivors-United States, 2013-2017. MMWR Morb Mortal Wkly Rep 2021;70:1–6.

540. Cuglievan B, Berkman A, Dibaj S, Wang J, Anderson CR, Livingston JA, et al. Impact of lagtime, health insurance type, and income status at diagnosis on the long-term survival of adolescent and young adult cancer patients. J Adolesc Young Adult Oncol 2021;10:164–74.

541. Doherty M, Gardner D, Finik J. The financial coping strategies of US cancer patients and survivors. Support Care Cancer 2021 Mar 18 [Epub ahead of print].

542. Leach CR, Kirkland EG, Masters M, Sloan K, Rees-Punia E, Patel AV, et al. Cancer survivor worries about treatment disruption and detrimental health outcomes due to the COVID-19 pandemic. J Psychosoc Oncol 2021;39:347–65.

543. Wimberly CE, Towry L, Caudill C, Johnston EE, Walsh KM. Impacts of COVID-19 on caregivers of childhood cancer survivors. Pediatr Blood Cancer 2021;68:e28943.

544. Davis C, Cadet T, Rune K, Wilson P, Banks J. Exploring the challenges in accessing care and support for cancer survivors in Australia during COVID-19. J Psychosoc Oncol 2021;39:479–84.

545. Brown M, O'Connor D, Murphy C, McClean M, McMeekin A, Prue G. Impact of COVID-19 on an established physical activity and behaviour change support programme for cancer survivors: an exploratory survey of the Macmillan Move More service for Northern Ireland. Support Care Cancer 2021 Apr 3 [Epub ahead of print].

546. Kato S, Kim KH, Lim HJ, Boichard A, Nikanjam N, Weihe E, et al. Real-world data from a molecular tumor board demonstrates improved outcomes with a precision N-of-One strategy. Nat Commun 2020;11:4965.

547. Tsimberidou AM, Hong DS, Wheler JJ, Falchook GS, Janku F, Naing A, et al. Long-term overall survival and prognostic score predicting survival: the IMPACT study in precision medicine. J Hematol Oncol 2019;12:145.

548. Zhang Q, Fu Q, Bai X, Liang T. Molecular profiling–based precision medicine in cancer: a review of current evidence and challenges. Front Oncol 2020;10:532403.

549. Morice PM, Leary A, Dolladille C, Chretien B, Poulain L, Gonzalez-Martin A, et al. Myelodysplastic syndrome and acute myeloid leukaemia in patients treated with PARP inhibitors: a safety meta-analysis of randomised controlled trials and a retrospective study of the WHO pharmacovigilance database. Lancet Haematol. 2021;8:e122–34.

550. Hirschey R, Nyrop KA, Mayer DK. Healthy behaviors: prevalence of uptake among cancer survivors. Clin J Oncol Nurs 2020;24:19–29.

551. Jassem J. Tobacco smoking after diagnosis of cancer: Clinical aspects. Transl Lung Cancer Res 2019;8(Suppl 1):S50–8.

552. Sheikh M, Mukeriya A, Shangina O, Brennan P, Zaridze D. Postdiagnosis smoking cessation and reduced risk for lung cancer progression and mortality. Ann Intern Med 2021 Jul 27 [Epub ahead of print].

553. Talluri R, Fokom Domgue J, Gritz ER, Shete S. Assessment of trends in cigarette smoking cessation after cancer diagnosis among US adults, 2000 to 2017. JAMA Netw Open 2020;3:e2012164.

554. Bassett JC, Matulewicz RS, Kwan L, McCarthy WJ, Gore JL, Saigal CS. Prevalence and correlates of successful smoking cessation in bladder cancer survivors. Urology 2021;153:236–43.

555. Vinci C. Cognitive behavioral and mindfulness-based interventions for smoking cessation: a review of the recent literature. Curr Oncol Rep 2020;22:58.

556. Asfar T, Koru-Sengul T, Annane D, McClure LA, Perez A, Antoni MA, et al. Reach versus effectiveness: the design and protocol of randomized clinical trial testing a smartphone application versus in-person mindfulness-based smoking cessation intervention among young cancer survivors. Contemp Clin Trials Commun 2021;22:100784.

557. Mardani A, Pedram Razi S, Mazaheri R, Haghani S, Vaismoradi M. Effect of the exercise programme on the quality of life of prostate cancer survivors: a randomized controlled trial. Int J Nurs Pract 2021;27:e12883.

558. Cannioto RA, Hutson A, Dighe S, McCann W, McCann SE, Zirpoli GR, et al. Physical activity before, during, and after chemotherapy for high-risk breast cancer: relationships with survival. J Natl Cancer Inst 2021;113:54–63.

559. Li Q, Lesseur C, Santella RM, Parada H, Teitelbaum S, Chen J. The associations of healthy lifestyle index with breast cancer incidence and mortality in a population-based study. Preprint from Research Square 2021 Jun 18.

560. Kwan ML, Lo JC, Laurent CA, Roh MJ, Tang L, Ambrosone CB, et al. A prospective study of lifestyle factors and bone health in breast cancer patients who received aromatase inhibitors in an integrated healthcare setting. J Cancer Surviv 2021 Feb 9 [Epub ahead of print].

561. Kim KH, Choi S, Kim K, Chang J, Kim SM, Kim SR, et al. Association between physical activity and subsequent cardiovascular disease among 5-year breast cancer survivors. Breast Cancer Res Treat 2021;188:203–14.

562. Miller JM, Sadak KT, Shahriar AA, Wilson NJ, Hampton M, Bhattacharya M, et al. Cancer survivors exercise at higher intensity in outdoor settings: the GECCOS trial. Pediatr Blood Cancer 2021;68:e28850.

563. Blount DS, McDonough DJ, Gao Z. Effect of wearable technology-based physical activity interventions on breast cancer survivors' physiological, cognitive, and emotional outcomes: a systematic review. J Clin Med 2021;10:2015.

564. Yurkiewicz IR, Simon P, Liedtke M, Dahl G, Dunn T. Effect of Fitbit and iPad wearable technology in health-related quality of life in adolescent and young adult cancer patients. J Adolesc Young Adult Oncol 2018;7:579–83.

565. Phillips S, Solk P, Welch W, Auster-Gussman L, Lu M, Cullather E, et al. A technology-based physical activity intervention for patients with metastatic breast cancer (Fit2ThriveMB): protocol for a randomized controlled trial. JMIR Res Protoc 2021;10:e24254.

566. Wang F, Cai H, Gu K, Shi L, Yu D, Zhang M, et al. Adherence to dietary recommendations among long-term breast cancer survivors and cancer outcome associations. Cancer Epidemiol Biomarkers Prev 2020;29:386–95.

567. Entwistle MR, Schweizer D, Cisneros R. Dietary patterns related to toal mortality and cancer mortality in the United States. Cancer Causes Control 2021 Aug 11 [Epub ahead of print].

568. Krok-Schoen JL, Pisegna J, Arthur E, Ridgway E, Stephens C, Rosko AE. Prevalence of lifestyle behaviors and associations with health-related quality of life among older female cancer survivors. Support Care Cancer 2021;29:3049–59.

REFERENCES

569. Teckie S, Wotman M, Marziliano A, Orner D, Yi J, Mulvany C, et al. Patterns of alcohol use among early head and neck cancer survivors: a cross-sectional survey study using the alcohol use disorders identification test (AUDIT). Oral Oncol 2021;119:105328.

570. Johnston EA, van der Pols JC, Ekberg S. Needs, preferences, and experiences of adult cancer survivors in accessing dietary information post-treatment: a scoping review. Eur J Cancer Care 2021;30:e13381.

571. Allicock M, Kendzor D, Sedory A, Gabriel KP, Swartz MD, thomas P, et al. A pilot and feasibility mobile health intervention to support healthy behaviors in African American breast cancer survivors. J Racial Ethn Heal Disparities 2021;8:157–65.

572. American Society of Clinical Oncology. Cancer.Net; healthy living. [cited 2021 Jul 10]. Available from: https://www.cancer.net/survivorship/healthy-living.

573. Rock CL, Doyle C, Demark-Wahnefried W, Meyerhardt J, Courneya KS, Schwartz AL, et al. Nutrition and physical activity guidelines for cancer survivors. CA Cancer J Clin 2012;62:242–74.

574. Centers for Disease Control and Prevention. Cancer survivors: guides to healthy living. [updated 2020 Dec 10; cited 2021 Jul 10]. Available from: https://www.cdc.gov/cancer/survivors/healthy-living-guides/index.htm.

575. National Comprehensive Cancer Network. NCCN guidelines for patients: survivorship care for healthy living, 2020. Available from: https://www.nccn.org/patients/guidelines/content/PDF/survivorship-hl-patient.pdf.

576. Rocque GB, Cleary JF. Palliative care reduces morbidity and mortality in cancer. Nat Rev Clin Oncol 2013;10:80–9.

577. Howie L, Peppercorn J. Early palliative care in cancer treatment: rationale, evidence and clinical implications. Ther Adv Med Oncol 2013;5:318–23.

578. Hausner D, Tricou C, Mathews J, Wadhwa D, Pope A, Swami N, et al. Timing of palliative care referral before and after evidence from trials supporting early palliative care. Oncologist 2021;26:332–40.

579. Ferrell BR, Chung V, Koczywas M, Smith TJ. Dissemination and implementation of palliative care in oncology. J Clin Oncol 2020;38:995–1001.

580. Mao JJ, Liou KT, Baser RE, Bao T, Panageas KS, Romero SAD, et al. Effectiveness of electroacupuncture or auricular acupuncture vs usual care for chronic musculoskeletal pain among cancer survivors the PEACE randomized clinical trial. JAMA Oncol 2021;7:720–7.

581. Sahgal A, Myrehaug SD, Siva S, Masucci L, Foote MC, Brundage M, et al. CCTG SC.24/TROG 17.06: a randomized phase II/III study comparing 24Gy in 2 stereotactic body radiotherapy (SBRT) fractions versus 20Gy in 5 conventional palliative radiotherapy (CRT) fractions for patients with painful spinal metastases. Int J Radiat Oncol Biol Phys 2020;108:1397–8.

582. Hui D, De La Rosa A, Chen J, Dibaj S, Guay MD, Heung Y, et al. State of palliative care services at US cancer centers: an updated national survey. Cancer 2020;126:2013–23.

583. Hui D, De La Rosa A, Chen J, Guay MD, Heung Y, Dibaj S, et al. Palliative care education and research at US cancer centers: a national survey. Cancer 2021;127:2139–47.

584. Mathews J, Zimmermann C. Palliative care services at cancer centres - room for improvement. Nat Rev Clin Oncol 2020;17:339–40.

585. Stal J, Nelson MB, Mobley EM, Ochoa CY, Milam JE, Freyer DR, et al. Palliative care among adult cancer survivors: knowledge, attitudes, and correlates. Palliat Support Care 2021 Jun 22 [Epub ahead of print].

586. Perry LM, Sartor O, Malhotra S, Alonzi S, Kim S, Voss HM, et al. Increasing readiness for early integrated palliative cncology care: development and initial evaluation of the EMPOWER 2 intervention. J Pain Symptom Manage 2021 Apr 20 [Epub ahead of print].

587. Lang-Rollin I, Berberich G. Psycho-oncology. Dialogues Clin Neurosci 2018;20:13–22.

588. Kingston T, Collie S, Hevey D, McCormick MM, Besani C, Cooney J, et al. Mindfulness-based cognitive therapy for psycho-oncology patients: an exploratory study. Ir J Psychol Med 2015;32:265–74.

589. Shaw JM, Sekelja N, Frasca D, Dhillon HM, Price MA. Being mindful of mindfulness interventions in cancer: a systematic review of intervention reporting and study methodology. Psychooncology 2018;27:1162–71.

590. Dos Santos M, Hardy-Léger I, Rigal O, Licaj I, Dauchy S, Levy C, et al. Cognitive rehabilitation program to improve cognition of cancer patients treated with chemotherapy: a 3-arm randomized trial. Cancer 2020;126:5328–36.

591. Lleras de Frutos M, Medina JC, Vives J, Casellas-Grau A, Marzo JL, Borras JM, et al. Video conference vs face-to-face group psychotherapy for distressed cancer survivors: a randomized controlled trial. Psychooncology 2020;29:1995–2003.

592. Oberoi S, Yang J, Woodgate RL, Niraula S, Banerji S, Israels SJ, et al. Association of mindfulness-based interventions with anxiety severity in adults with cancer: a systematic review and meta-analysis. JAMA Netw Open 2020;3:e2012598.

593. Weaver SJ, Jacobsen PB. Cancer care coordination: opportunities for healthcare delivery research. Transl Behav Med 2018;8:503–8.

594. Gallicchio L, Tonorezos E, de Moor JS, Elena J, Farrell M, Green P, et al. Evidence gaps in cancer survivorship care: a report from the 2019 National Cancer Institute Cancer Survivorship Workshop. JNCI J Natl Cancer Inst 2021 Mar 23 [Epub ahead of print].

595. Larson JL, Rosen AB, Wilson FA. The effect of telehealth interventions on quality of life of cancer survivors: a systematic review and meta-analysis. Health Informatics J 2020;26:1060–78.

596. Kenney LB, Vrooman LM, Lind ED, Brace-O'Neill J, Mulder JE, Nekhlyudov L, et al. Virtual visits as long-term follow-up care for childhood cancer survivors: patient and provider satisfaction during the COVID-19 pandemic. Pediatr Blood Cancer 2021;68:e28927.

597. Salmi L, Dong ZJ, Yuh B, Walker J, DesRoches CM. Open notes in oncology: patient versus oncology clinician views. Cancer Cell 2020;38:767–8..

598. Junkins CC, Kent E, Litzelman K, Bevans M, Cannady RS, Rosenberg AR. Cancer across the ages: a narrative review of caregiver burden for patients of all ages. J Psychosoc Oncol 2020;38:782–98.

599. Borsky AE, Zuvekas SH, Kent EE, de Moor JS, Ngo-Metzger Q, Soni A. Understanding the characteristics of US cancer survivors with informal caregivers. Cancer 2021;127:2752–61.

600. Given BA, Given CW, Sherwood PR. Family and caregiver needs over the course of the cancer trajectory. J Support Oncol 2012;10:57–64.

601. Harrison R, Raman M, Walpola RL, Chauhan A, Sansom-Daly UM. Preparing for partnerships in cancer care: an explorative analysis of the role of family-based caregivers. BMC Heal Serv Res 2021;21:620.

602. Fisher AP, Patronick J, Gerhardt CA, Radonovich K, Salloum R, Wade SL. Impact of COVID-19 on adolescent and emerging adult brain tumor survivors and their parents. Pediatr Blood Cancer 2021;68:e29116.

603. Renna ME, Quintero JM, Fresco DM, Mennin DS. Emotion regulation therapy: a mechanism-targeted treatment for disorders of distress. Front Psychol 2017;8:98.

604. O'Toole MS, Mennin DS, Applebaum A, Weber B, Rose H, Fresco DM, et al. A randomized controlled trial of emotion regulation therapy for psychologically distressed caregivers of cancer patients. JNCI Cancer Spectr 2020;4:pkz074.

605. Rodriguez H, Zenklusen JC, Staudt LM, Doroshow JH, Lowy DR. The next horizon in precision oncology: proteogenomics to inform cancer diagnosis and treatment. Cell 2021;184:1661–70.

606. Chen YJ, Roumeliotis TI, Chang YH, Chen CT, Han CL, Lin MH, et al. Proteogenomics of non-smoking lung cancer in East Asia delineates molecular signatures of pathogenesis and progression. Cell 2020;182:226–44.

607. Krug K, Jaehnig EJ, Satpathy S, Blumenberg L, Karpova A, Anurag M, et al. Proteogenomic landscape of breast cancer tumorigenesis and targeted therapy. Cell 2020;183:1436–56.

608. Petralia F, Tignor N, Reva B, Koptyra M, Chowdhury S, Rykunov D, et al. Integrated proteogenomic characterization across major histological types of pediatric brain cancer. Cell 2020;183:1962–85.

609. Huang C, Chen L, Savage SR, Eguez RV, Dou Y, Li Y, et al. Proteogenomic insights into the biology and treatment of HPV-negative head and neck squamous cell carcinoma. Cancer Cell 2021;39:361–79.

610. Satpathy S, Krug K, Beltran PMJ, Savage SR, Petralia F, Kumar-Sinha C, et al. A proteogenomic portrait of lung squamous cell carcinoma. Cell 2021;184:4348–71.

611. Satpathy S, Jaehnig EJ, Krug K, Kim BJ, Saltzman AB, Chan DW, et al. Microscaled proteogenomic methods for precision oncology. 2020;11:532.

612. Yoo S, Shi Z, Wen B, Kho S, Pan R, Feng H, et al. A community effort to identify and correct mislabeled samples in proteogenomic studies. Patterns 2021;2:100245.

613. Topol EJ. High-performance medicine: the convergence of human and artificial intelligence. Nat Med 2019;25:44–56.

614. Ho D. Artificial intelligence in cancer therapy. Science 2020;367:982–3.

615. Sahoo D, Swanson L, Sayed IM, Katkar GD, Ibeawuchi SR, Mittal Y, et al. Artificial intelligence guided discovery of a barrier-protective therapy in inflammatory bowel disease. Nat Commun 2021;12:4246.

616. Savage N. Tapping into the drug discovery potential of AI. Biopharma Dealmakers 2021 May 27. Available from: https://www.nature.com/articles/d43747-021-00045-7.

617. Vamathevan J, Clark D, Czodrowski P, Dunham I, Ferran E, Lee G, et al. Applications of machine learning in drug discovery and development. Nat Rev Drug Discov 2019;18:463–77.

618. Senior AW, Evans R, Jumper J, Kirkpatrick J, Sifre L, Green T, et al. Improved protein structure prediction using potentials from deep learning. Nature 2020;577:706–10.

619. Service RF. 'The game has changed.' AI triumphs at solving protein structures. Science 2020;370:1144–5.

620. Tunyasuvunakool K, Adler J, Wu Z, Green T, Zielinski M, Zidek A, et al. Highly accurate protein structure prediction for the human proteome. Nature 2021 Jul 22 [Epub ahead of print].

621. Jumper J, Evans R, Pritzel A, Green T, Figurnov M, Ronneberger O, et al. Highly accurate protein structure prediction with AlphaFold. Nature 2021 Jul 15 [Epub ahead of print].

622. Exscientia announces first AI-designed immuno-oncology drug to enter clinical trials. [cited 2021 Jul 10]. Available from: https://www.exscientia.ai/news-insights/exscientia-first-ai-designed-immuno-oncology-drug-trial.

623. Payne A, Fons P, Alt I, Van Ham J, Taubert C, Bell A, et al. 1731 - EXS21546, a non-CNS penetrant A 2A R-selective antagonist for anti-cancer immunotherapy. Session PO.IM02.07, Immunomodulatory Agents and Interventions. 2021 April 10. AACR Annual Meeting 2021. Available from: https://www.abstractsonline.com/pp8/#!/9325/presentation/2832.

624. NIH, U.S. National Library of Mecine, Clinical Trials.gov. 3-part study to assess safety, tolerability, pharmacokinetics and pharmacodynamics of EXS21546. [updated 2021 Jan 29; cited 2021 July 10]. Available from: https://clinicaltrials.gov/ct2/show/NCT04727138.

625. Liu R, Rizzo S, Whipple S, Pal N, Pineda AL, Lu M, et al. Evaluating eligibility criteria of oncology trials using real-world data and AI. 2021;592:629–33.

626. Manz CR, Chen J, Liu M, Chivers C, Regli SH, Braun J, et al. Validation of a machine learning algorithm to predict 180-day mortality for outpatients with cancer. JAMA Oncol 2020;6:1723–30.

627. Song J, Wang L, Ng NN, Zhao M, Shi J, Wu N, et al. Development and validation of a machine learning model to explore tyrosine kinase inhibitor response in patients with stage IV EGFR variant-positive non-small cell lung cancer. JAMA Netw Open 2020;3:e2030442.

628. Ioannou GN, Tang W, Beste LA, Tincopa MA, Su GL, Van T, et al. Assessment of a deep learning model to predict hepatocellular carcinoma in patients with hepatitis C cirrhosis. JAMA Netw Open 2020;3:e2015626.

629. Tseng YJ, Wang HY, Lin TW, Lu JJ, Hsieh CH, Liao CT. Development of a machine learning model for survival risk stratification of patients with advanced oral cancer. JAMA Netw Open 2020;3:e2011768.

630. Adamson AS, Smith A. Machine learning and health care disparities in dermatology. JAMA Dermatol 2018;154:1247–8.

631. Gao Y, Cui Y. Deep transfer learning for reducing health care disparities arising from biomedical data inequality. Nat Commun 2020;11:5131.

632. Zou J, Schiebinger L. Ensuring that biomedical AI benefits diverse populations. EBioMedicine 2021;67:103358.

633. Hsiue EHC, Wright KM, Douglass J, Hwang MS, Mog BJ, Pearlman AH, et al. Targeting a neoantigen derived from a common TP53 mutation. Science 2021;371:eabc8697.

634. Douglass J, Hsiue EHC, Mog BJ, Hwang MS, DiNapoli SR, Pearlman AH, et al. Bispecific antibodies targeting mutant RAS neoantigens. Sci Immunol 2021;6:eabd5515.

635. Samarasinghe KTG, Crews CM. Targeted protein degradation: a promise for undruggable proteins. Cell Chem Biol 2021;28:934–51.

636. Dang CV, Reddy EP, Shokat KM, Soucek L. Drugging the "undruggable" cancer targets. Nat Rev Cancer 2017;17:502–8.

REFERENCES

637. Coleman N, Rodon J. Taking aim at the undruggable. Am Soc Clin Oncol Educ Book 2021;41:1–8.

638. Mullard A. Targeted protein degraders crowd into the clinic. Nat Rev Drug Discov 2021;20:247–50.

639. Bery N, Miller A, Rabbitts T. A potent KRAS macromolecule degrader specifically targeting tumours with mutant KRAS. Nat Commun 2020;11:3233.

640. Wang C, Zhang J, Yin J, Gan Y, Xu S, Gu Y, et al. Alternative approaches to target Myc for cancer treatment. Signal Transduct Target Ther 2021;6:117.

641. Hines J, Lartigue S, Dong H, Qian Y, Crews CM. MDM2-recruiting PROTAC offers superior, synergistic antiproliferative activity via simultaneous degradation of BRD4 and stabilization of p53. Cancer Res 2019;79:251–62.

642. Roberts MC, Kennedy AE, Chambers DA, Khoury MJ. The current state of implementation science in genomic medicine: opportunities for improvement. Genet Med 2017;19:858–63.

643. Oh A, Vinson CA, Chambers DA. Future directions for implementation science at the National Cancer Institute: Implementation Science Centers in Cancer Control. Transl Behav Med 2021;11:669–75.

644. Neta G, Clyne M, Chambers DA. Dissemination and implementation research at the national cancer institute: a review of funded studies (2006-2019) and opportunities to advance the field. Cancer Epidemiol Biomarkers Prev 2021;30:260–7.

645. NIH, Natinoal Cancer Institute. Implementation science - opportunities in cancer research. [cited 2021 Aug 9]. Available from: https://www.cancer.gov/research/areas/treatment/implementation-science.

646. Mitchell SA, Chambers DA. Leveraging implementation science to improve cancer care delivery and patient outcomes. J Oncol Pract 2017;13:523–9.

647. Natinal Institutes of Health. The NIH mission – it's about life. [updated 2021 Apr 16; cited 2021 Aug 14]. Available from: https://www.nih.gov/news-events/videos/nih-mission-its-about-life.

648. Carlisle BG. Clinical trials stopped by COVID-19. [updated 2021 Jan 29; cited 2021 Jul 9]. Available from: https://covid19.bgcarlisle.com/.

649. Upadhaya S, Yu JX, Hodge J, Campbell J. COVID-19 impact on oncology clinical trials: a 1-year analysis. Nat Rev Drug Discov 2021;20:415.

650. Bauman J. Pandemic cost NIH $16 billion in delayed, lost medical research. Bloomberg Law 2021 Mar 19. Available from: https://news.bloomberglaw.com/pharma-and-life-sciences/pandemic-cost-nih-16-billion-in-delayed-lost-medical-research.

651. Garrido P, Adjei AA, Bajpai J, Banerjee S, Brghoff AS, Choo SP, et al. Has COVID-19 had a greater impact on female than male oncologists? Results of the ESMO Women for Oncology (W4O) Survey. ESMO Open 2021;6:100131.

652. Langin K. Pandemic hits scientist parents hard. Science2020;369:609–10.

653. Gewin V. The career cost of COVID-19 to female researchers, and how science should respond. Nature 2020;583:867–9.

654. NIH, National Cancer Institute. NCI director's message: fiscal year 2022 annual plan & budget proposal. 2020 Aug 31. [cited 2021 July 9]. Available from: https://www.cancer.gov/research/annual-plan/directors-message.

655. NIH, RePORT. Success rates. [cited 2021 Jul 9]. Available from: https://report.nih.gov/funding/nih-budget-and-spending-data-past-fiscal-years/success-rates.

656. Stevens KR, Masters KS, Imoukhuede PI, Haynes KA, Setton LA, Cosgriff-Hernandez E, et al. Fund Black scientists. Cell 2021;184:56–5.

657. Taffe MA, Gilpin NW. Equity, diversity and inclusion racial inequity in grant funding from the us national institutes of health. Elife 2021;10:e65697.

658. Single digits: Black, Hispanic scientists strikingly underrepresented at NCI among senior workforce and grantees. Cancer Letter 2021;47. [cited 2021 Aug 15]. Available from: https://cancerletter.com/health-equity/20210702_1/.

659. Oliveira DFM, Ma Y, Woodruff TK, Uzzi B. Comparison of National Institutes of Health Grant Amounts to First-Time Male and Female Principal Investigators. JAMA 2019;321:898-900.

660. Carr PL, Raj A, Kaplan SE, Terrin N, Breeze JL, Freund KM. Gender differences in academic medicine: Retention, rank, and leadership comparisons from the national faculty survey. Acad Med. 2018;93:1694-1699.

661. Wadman M. NIH 'high risk, high reward' awardees skew male—again. Science 2019;366:290..

662. United for Medical Research. NIH's role in sustaining the U.S. economy. [updated 2021 Mar 24; cited 2021 Jul 9]. Available from: https://www.unitedformedicalresearch.org/reports/nihs-role-in-sustaining-the-u-s-economy/.

663. Reynolds AJ, Ou SR, Temple JA. A multicomponent, preschool to third grade preventive intervention and educational attainment at 35 years of age. JAMA Pediatr 2018;172:247–56.

664. National Cancer Institute, National Institutes of Health, Center to Reduce Cancer Health Disparities. Continuing umbrella of research experiences (CURE). [cited 2021 Jul 11]. Available from: https://www.cancer.gov/about-nci/organization/crchd/diversity-training/cure/cure-infographic.pdf.

665. Science Education Partnership Award. [cited 2021 Jul 9]. Available from: https://nihsepa.org/.

666. The University of Arizona, Q-Cubed. Statistics & evaluation. [cited 2021 Jul 9]. Available from: https://ignorance.medicine.arizona.edu/results/statistics-evaluation.

667. Andriole DA, Jeffe DB. Predictors of full-time faculty appointment among MD-PhD program graduates: a national cohort study. Med Educ Online 2016;21:30941.

668. Conte ML, Omary MB. NIH career development awards: conversion to research grants and regional distribution. J Clin Invest 2018;128:5187–90.

669. NIH, National Cancer Institute. MERIT award (R37). [updated 2020 Nov 5; cited 2021 Jul 9]. Available from: https://www.cancer.gov/grants-training/grants-funding/funding-opportunities/merit.

670. National Institutes of Health. Faculty institutional recruitment for sustainable transformation (FIRST). [updated 2021 Aug 17; cited 2021 Jul 9]. Available from: https://commonfund.nih.gov/first.

671. Krukowski RA, Jagsi R, Cardel MI. Academic productivity differences by gender and child age in science, technology, engineering, mathematics, and medicine faculty during the COVID-19 pandemic. J Womens Health 2021;30:341–7.

672. Cardel MI, Dhurandhar E, Yarar-Fisher C, Foster M, Hidalgo B, McClure LA, et al. Turning chutes into ladders for women faculty: a review and roadmap for equity in academia. J Womens Health 2020;29:721–33.

673. National Academies of Sciences, Engineering and Medicine; Policy and Global Affairs; Committee on Women in Science, Engineering, and Medicine; Committee on Investigating the Potential Impacts of COVID-19 on the Careers of Women in Academic Science, Engineering, and Medicine. Dahlberg ML, Higginbotham E, editors. Impact of COVID-19 on the careers of women in academic sciences, engineering, and medicine. Washington (DC): National Academies Press; 2021.

674. de Claro RA, Gao JJ, Kim T, Kluetz PG, Theoret MR, Beaver JA, et al. U.S. Food and Drug Administration: initial experience with the real-time oncology review program. Clin Cancer Res 2021;27:11–4.

675. de Claro RA, Spillman D, Hotaki LT, Shum M, Mouawad LS, Santos GML, et al. Project Orbis: global collaborative review program. Clin Cancer Res 2020;26:6412–6.

676. U.S. Food & Drug Administration. 2020 Annual Report: oncology center of excellence. [cited Aug 13]. Available from: https://www.fda.gov/media/145613/download.

677. Bleyer A, Tai E, Siegel S. Role of clinical trials in survival progress of American adolescents and young adults with cancer-and lack thereof. Pediatr Blood Cancer 2018;65:e27074.

678. Hunger SP, Lu X, Devidas M, Camitta BM, Gaynon PS, Winick NJ, et al. Improved survival for children and adolescents with acute lymphoblastic leukemia between 1990 and 2005: a report from the Children's Oncology Group. J Clin Oncol 2012;30:1663–9.

679. Valecha G, Thumallapally N, El Bitar S, Terjanian TO, Madrigal L, Longo L, et al. Clinical trial awareness in oncology patients of diverse ethnic background: a single-institution analysis. J Clin Oncol 2020;38(15_suppl):e19217.

680. Han JJ, Kim JW, Suh KJ, Kim JW, Kim SH, Kim YJ, et al. Clinical characteristics and outcomes of patients enrolled in clinical trials compared with those of patients outside clinical trials in advanced gastric cancer. Asia Pac J Clin Oncol 2019;15:158–65.

681. Koo KC, Lee JS, Kim JW, Han KS, Lee KS, Kim DK, et al. Impact of clinical trial participation on survival in patients with castration-resistant prostate cancer: a multi-center analysis. BMC Cancer 2018;18:468.

682. Narui K, Ohno S, Mukai H, Hozumi Y, Miyoshi Y, Yoshino H, et al. Overall survival of participants compared to non-participants in a randomized-controlled trial (SELECT BC): a prospective cohort study. J Clin Oncol 2016;34(15_suppl):2527.

683. Unger JM, Hershman DL, Till C, Minasian LM, Osarogiagbon RU, Fleury ME, et al. "When offered to participate": a systematic review and meta-analysis of patient agreement to participate in cancer clinical trials. J Natl Cancer Inst 2021;113:244–57.

684. Unger JM, Vaidya R, Hershman DL, Minasian LM, Fleury ME. Systematic review and meta-analysis of the magnitude of structural, clinical, and physician and patient barriers to cancer clinical trial participation. J Natl Cancer Inst 2019;111:245–55.

685. Faulk KE, Anderson-Mellies A, Cockburn M, Green AL. Assessment of enrollment characteristics for Children's Oncology Group (COG) upfront therapeutic clinical trials 2004-2015. PLoS One 2020;15:e0230824.

686. Aristizabal P, Singer J, Cooper R, Wells KJ, Nodora J, Milburn M, et al. Participation in pediatric oncology research protocols: racial/ethnic, language and age-based disparities. Pediatr Blood Cancer 2015;62:1337–44.

687. Borno HT, Zhang L, Siegel A, Chang E, Ryan CJ. At what cost to clinical trial enrollment? A retrospective study of patient travel burden in cancer clinical trials. Oncologist 2018;23:1242–9.

688. Largent EA, Lynch HF. Addressing financial barriers to enrollment in clinical trials. JAMA Oncol 2018;4:913–4.

689. Nipp RD, Lee H, Gorton E, Lichtenstein M, Kuchukhidze S, Park E, et al. Addressing the financial burden of cancer clinical trial participation: longitudinal effects of an equity intervention. Oncologist 2019;24:1048–55.

690. Lungevity Foundation. LUNGevity barriers to clinical trial participation as perceived by lung cancer patients and caregivers. Available from: https://www.lungevity.org/sites/default/files/file-uploads/Barriers-to-Clinical-Trial-Participation-Study_0.pdf.

691. Unger JM, Cook E, Tai E, Bleyer A. The role of clinical trial participation in cancer research: barriers, evidence, and strategies. Am Soc Clin Oncol Educ Book 2016;35:185–98.

692. U.S. Food & Drug Adminstration. Clinical trial conduct during the COVID-19 pandemic. [updated 2020 Jun 1; cited 2021 Aug 13]. Available from: https://www.fda.gov/drugs/coronavirus-covid-19-drugs/clinical-trial-conduct-during-covid-19-pandemic.

693. Sharpe K, Scheid K. The benefits of patient navigation. J Oncol Nav Surv 2021;9. Available from: https://www.jons-online.com/issues/2018/october-2018-vol-9-no-10/1998-the-benefits-of-patient-navigation.

694. Natale-Pereira A, Enard KR, Nevarez L, Jones LA. The role of patient navigators in eliminating health disparities. Cancer 2011;117(15 Suppl):3543–52..

695. Freeman HP, Rodriguez RL. History and principles of patient navigation. Cancer 2011;117(15 Suppl):3539–42.

696. Osundina F, Garfield K, Downer S. Patient navigation in cancer care review of payment models for a sustainable future. American Cancer Society, Inc. No. 08051. Available from: http://navigationroundtable.org/wp-content/uploads/Patient-Navigation-in-Cancer-Care-Review-of-Payment-Models_FINAL.pdf.

697. U.S. Food & Drug Adminstration. Enhancing the diversity of clinical trial populations - eligibility criteria, enrollment practices, and trial designs guidance for industry, November 2020. [updated 2020 Nov 13; cited 2021 Jul 9]. Available from: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/enhancing-diversity-clinical-trial-populations-eligibility-criteria-enrollment-practices-and-trial.

698. U.S. Preventive Services Task Force. Screening for breast cancer. [updated 2021 Apr 29; cited 2021 Jul 9]. Available from: https://www.uspreventiveservicestaskforce.org/uspstf/draft-update-summary/breast-cancer-screening1.

699. Centers for Disease Control and Prevention. How many cancers are linked with HPV each year? [updated 2020 Sep 3; cited 2021 Jul 11]. Available from: https://www.cdc.gov/cancer/hpv/statistics/cases.htm.

700. Elam-Evans LD, Yankey D, Singleton JA, Sterrett N, Markowitz LE, Williams CL, et al. National, regional, state, and selected local area vaccination coverage among adolescents aged 13–17 years - United States, 2019. MMWR Morb Mortal Wkly Rep 2020;69:1109–16.

REFERENCES

701. Truth Initiative. E-cigarettes drive overall youth tobacco use to highest rate in decades. 2019 Dec 9. [cited 2021 Jul 9]. Available from: https://truthinitiative.org/research-resources/emerging-tobacco-products/e-cigarettes-drive-overall-youth-tobacco-use-highest.

702. U.S. Food & Drug Administration. Youth tobacco use: results from the National Youth Tobacco Survey. [updated 2020 Dec 22; cited 2021 Jul 9]. Available from: https://www.fda.gov/tobacco-products/youth-and-tobacco/youth-tobacco-use-results-national-youth-tobacco-survey.

703. Lee YO, Glantz SA. Menthol: putting the pieces together. Tob Control 2011;20(Suppl 2):ii1–7.

704. Okuyemi KS, Faseru B, Cox LS, Bronars CA, Ahluwalia JS. Relationship between menthol cigarettes and smoking cessation among African American light smokers. Addiction 2007;102:1979–86.

705. Ross KC, Dempsey DA, St Helen G, Delucchi K, Benowitz NL. The influence of puff characteristics, nicotine dependence, and rate of nicotine metabolism on daily nicotine exposure in African American smokers. Cancer Epidemiol Prev Biomarkers 2016;25:936–43.

706. Villanti AC, Collins LK, Niaura RS, Gagosian SY, Abrams DB. Menthol cigarettes and the public health standard: a systematic review. BMC Public Heal 2017;17:983.

707. Brody AL, Mukhin AG, La Charite J, Ta K, Farahi J, Sugar CA, et al. Up-regulation of nicotinic acetylcholine receptors in menthol cigarette smokers. Int J Neuropsychopharmacol 2013;16:957–66.

708. Leas EC, Benmarhinia T, Strong DR, Pierce JP. Effects of menthol use and transitions in use on short-term and long-term cessation from cigarettes among US smokers. Tob Control 2021 Jul 6 [Epub ahead of print].

709. Campaign for Tobacco-Free Kids. Stopping menthol, saving lives: ending big tobacco's predatory marketing to black communities. [updated 2021 Feb 24]. Available from: https://www.tobaccofreekids.org/what-we-do/industry-watch/menthol-report.

710. U.S. Food & Drug Administration. FDA commits to evidence-based actions aimed at saving lives and preventing future generations of smokers. [updated 2021 Apr 29; cited 2021 Jul 9]. Available from: https://www.fda.gov/news-events/press-announcements/fda-commits-evidence-based-actions-aimed-saving-lives-and-preventing-future-generations-smokers.

711. Maloney J. Biden administration considering rule to cut nicotine in cigarettes. [updated 2021 Apr 19; cited 2021 Jul 9]. Wall Street Journal. Available from: https://www.wsj.com/articles/biden-administration-considering-rule-to-cut-nicotine-in-cigarettes-11618859564.

712. Apelberg BJ, Feirman SP, Salazar E, Corey CG, Ambrose BK, Paredes A, et al. Potential public health effects of reducing nicotine levels in cigarettes in the United States. N Engl J Med 2018;378:1725–33.

713. NIH, National Cancer Institute. Cancer in children and adolescents. [updated 2021 Apr 20; cited 2021 Jul 9]. Available from: https://www.cancer.gov/types/childhood-cancers/child-adolescent-cancers-fact-sheet.

714. Reaman G, Karres D, Ligas F, Lesa G, Casey D, Ehrlich L, et al. Accelerating the global development of pediatric cancer drugs: a call to coordinate the submissions of pediatric investigation plans and pediatric study plans to the European Medicines Agency and US Food and Drug Administration. J Clin Oncol 2020;38:4227–30.

715. Oncology drug shortages persist. Cancer Discov 2020;10:6.

716. U.S. Food & Drug Administration. Drug shortages: root causes and potential solutions. [updated 2021 Mar 11; cited 2021 Aug 13]. Available from: https://www.fda.gov/drugs/drug-shortages/report-drug-shortages-root-causes-and-potential-solutions.

717. Doubeni C, Simon M, Krist AH. Addressing systemic racism through clinical preventive service recommendations from the US Preventive Services Task Force. JAMA 2021;325:627–8.

718. Chou R, Blazina I, Bougatsos C, Holmes R, Selph S, Grusing S, et al. Screening for hepatitis B virus infection in nonpregnant adolescents and adults: updated evidence report and systematic review for the US Preventive Services Task Force. JAMA 2020;324:2423–36.

719. Lin JS, Perdue LA, Henrikson NB, Bean SI, Blasi PR. Screening for colorectal cancer: updated evidence report and systematic review for the US Preventive Services Task Force. JAMA 2021;325:1978–97.

720. Centers for Disease Control and Prevention. National Breast and Cervical Cancer Early Detection Program [updated 2021, Aug 31; cited 2021 Sep 11]. Available from: https://www.cdc.gov/cancer/nbccedp/index.htm

721. Patel KG, Borno HT, Seligman HK. Food insecurity screening: a missing piece in cancer management. Cancer 2019;125:3494–501.

722. Moss K, Dawson L, Long M, Kates J, Musumeci MB, Cubanski J, et al. The Families First Coronavirus Response Act: summary of key provisions. KFF 2020 Mar 23. Available from: https://www.kff.org/coronavirus-covid-19/issue-brief/the-families-first-coronavirus-response-act-summary-of-key-provisions/.

723. Center on Budget and Policy Priorities. States are using much-needed temporary flexibility in SNAP to respond to COVID-19 challenges. [updated 2021 Aug 6; cited 2021 July 9]. Available from: https://www.cbpp.org/research/food-assistance/states-are-using-much-needed-temporary-flexibility-in-snap-to-respond-to.

724. Centers for Disease Control and Prevention.REACH program impact. [updated 2020 Mar 10; cited 2021 Aug 20]. Available from: https://www.cdc.gov/nccdphp/dnpao/state-local-programs/reach/program_impact/index.htm.

725. Finegold K, Conmy A, Chu RC, Bosworth A, Sommers BD. Trends in the U.S. uninsured population, 2010-2020. Department of Health and Human Services, Office of Health Policy Issue Brief, 2021 Feb 11. Available from: https://aspe.hhs.gov/sites/default/files/private/pdf/265041/trends-in-the-us-uninsured.pdf.

726. Status of state Medicaid expansion decisions: interactive map. [cited 2021 Jul 9]. KFF 2021 Aug 10. Available from: https://www.kff.org/medicaid/issue-brief/status-of-state-medicaid-expansion-decisions-interactive-map/.

727. Su CT, Okullo D, Hingtgen S, Levine DA, Goold SD. Affordable Care Act and cancer survivors' financial barriers to care: analysis of the National Health Interview Survey, 2009-2018. JCO Oncol Pract 2021 Jul 13 [Epub ahead of print].

728. Guth M, Garfield R, Rudowitz R, Damico A. The status of Medicaid expansion in Missouri and implications for coverage and cost. [cited 2021 Jul 9]. KFF 2021 Jun 30. Available from: https://www.kff.org/policy-watch/status-of-medicaid-expansion-in-missouri-and-implications-for-coverage-and-cost/.

729. Corallo B, Rudowitz R. Analysis of recent national trends in Medicaid and CHIP enrollment. [cited 2021 Jul 9]. KFF 2021 Aug 16. Available from: https://www.kff.org/coronavirus-covid-19/issue-brief/analysis-of-recent-national-trends-in-medicaid-and-chip-enrollment/.

730. Feinstein D. S.Res.253 - a resolution supporting the designation of May 2021 as "National Cancer Research Month". 117th Congress (2021-2022). [cited 2021 Aug 13]. Available from: https://www.congress.gov/bill/117th-congress/senate-resolution/253.

731. Cancer Researh Catalyst staff. Letter from President Biden to the AACR recognizes National Cancer Research Month. [cited 2021 Aug 13]. American Association for Cancer Research 2021 May 25. Available from: https://www.aacr.org/blog/2021/05/25/letter-from-president-biden-to-the-aacr-recognizes-national-cancer-research-month/.

732. Congressional Management Foundation. Citizen-centric advocacy: the untapped power of constituent engagement, 2017. Available from: https://www.congressfoundation.org/projects/communicating-with-congress/citizen-centric-advocacy-2017.

733. Ballast Research. Washington insights review: the new advocacy environment. 2021 Jan. Available from: https://www.ballastresearch.com/wp-content/uploads/2021/01/2020-Washington-Insights-Review-1.pdf.

734. English P. The power of patient advocacy in drug development. [cited 2021 Jul 9]. Advara 2021 May 27. Available from: https://www.advarra.com/blog/the-power-of-patient-advocacy-in-drug-development/.

735. Deverka PA, Bangs R, Kreizenbeck K, Delaney DM, Hershman DL, Blanke CD, et al. A new framework for patient engagement in Cancer Clinical Trials Cooperative Group studies. JNCI J Natl Cancer Inst 2018;110:553–9.

736. Paskett ED, Hiatt RA. Catchment areas and community outreach and engagement: the new mandate for NCI-designated cancer centers. Cancer Epidemiol Biomarkers Prev 2018;27:517–9.

737. University of Michigan Library. Research guides: COVID-19 (novel coronavirus): webinars & online learning. Available from: https://guides.lib.umich.edu/covid19/onlinelearning.

738. Emory University School of Medicine, Emergency Medicine. COVID-19 response. Available from: https://med.emory.edu/departments/emergency-medicine/patient-care/covid-19/index.html.

739. Irving Institute for Clinical and Translational Research. Health education lectures for lay community. Available from: https://www.irvinginstitute.columbia.edu/services/health-education-lectures-lay-community.

740. National Science Policy Network. FY20 annual report, 2019-2020. Available from: https://drive.google.com/file/d/1SjU2weBqL0BPWHzYkmeyP4Z1yFi44Vj_/view.

741. Dartmouth, Office of the Registrar. Organization, regulations, and courses 2020-21; PEMM 132 clinical management of cancer. [cited 2021 Aug 13]. Available from: http://dartmouth.smartcatalogiq.com/current/orc/Departments-Programs-Graduate/Program-in-Experimental-and-Molecular-Medicine/PEMM-Experimental-and-Molecular-Medicine/100/PEMM-132.

742. National Coalition for Cancer Survivorship. 2020 state of Cancer Survivorship Survey. [published 2021 Feb 1; cited 2021 Sep 11]. Availabale from https://canceradvocacy.org/policy/2020-state-of-cancer-survivorship-survey/

GLOSSARY*

A

Acute myeloid leukemia (AML) A fast-growing cancer in which the bone marrow makes abnormal myeloblasts (a type of white blood cell), red blood cells, or platelets. It is also called acute myeloblastic leukemia, acute myelogenous leukemia, and acute nonlymphocytic leukemia.

Adjuvant therapy Additional cancer treatment that is given after the primary treatment is completed to lower the risk that the cancer will come back. Adjuvant therapy may include chemotherapy, radiotherapy, hormone therapy, targeted therapy, or immunotherapy.

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.

Basal cell carcinoma A form of skin cancer that begins in a type of cell in the skin that produces new skin cells as old ones die off. It is the most common cancer, but it rarely metastasizes (spreads to other parts of the body). Also called basal cell cancer.

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.

BRCA1/2 (BReast CAncer Genes 1 and 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.

* This list contains some of the specialized terms pertinent to the *AACR Cancer Progress Report 2021*. The NCI has been used as the primary source for most definitions.

Chemotherapy The use of chemical substances to kill or slow the growth of cancer cells.

Chimeric antigen receptor (CAR) A receptor created in the laboratory that is designed to bind to certain proteins on cancer cells. It is then added to immune cells called T cells taken from cancer patients. This helps the T cells find and kill cancer cells that have a specific protein that the CAR is designed to bind to.

Chromosomal translocation Genomic alteration in which a whole chromosome or segment of a chromosome becomes attached to or interchanged with another whole chromosome or segment. Chromosomal translocations can, in some cases, fuel cancer.

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.

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.

Department of Defense (DoD) The Department of Defense funds a myriad of cancer research initiatives through the Congressionally Directed Medical Research Programs (CDMRP). The CDMRP, created by a congressional mandate in 1992, fills research gaps by funding high impact, high risk and high gain projects to transform health care for service members and the American public through innovative and impactful research.

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.

Endometrial cancer Cancer that forms in the tissue lining the uterus.

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 ERBB2 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

Five-year survival rate The percentage of people in a specific group, for example, people diagnosed with a certain type of cancer or those who started a certain treatment, who are alive 5 years after they were diagnosed with or started treatment for a disease, such as cancer. The disease may or may not have come back.

GLOSSARY

Financial toxicity A term used to describe financial problems a patient has related to the cost of cancer care.

Food and Drug Administration (FDA) An agency in the U.S. federal government whose mission is to protect public health by making sure that food, cosmetics, and nutritional supplements are safe to use and truthfully labeled. The FDA also makes sure that drugs, medical devices, and equipment are safe and effective, and that blood for transfusions and transplant tissue are safe.

G

Gastric cancer Cancer that arises in cells lining the stomach. Cancers starting in different sections of the stomach may cause different symptoms and often have different outcomes. Infection with the bacterium *Helicobacter pylori* is a major cause of gastric cancer, except for gastric cancers arising in the top portion of the stomach, called the cardia.

Gastroesophageal junction adenocarcinoma Cancer that arises in cells located where the esophagus (the tube that connects the throat and stomach) joins the stomach. This gastroesophageal junction includes the top portion of the stomach, called the cardia.

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.

H

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.

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.

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).

Mesothelioma A tumor that affects the lining of the chest or abdomen. Exposure to asbestos particles increases the risk of developing malignant mesothelioma.

MET A gene that makes a protein that is involved in sending signals within cells and in cell growth and survival. Altered forms of the MET gene may cause abnormal cells to grow and spread in the body.

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.

Microsatellite instability (MSI) A change that occurs in the DNA of certain cells (such as tumor cells) in which the number of repeats of microsatellites (short, repeated sequences of DNA) is different than the number of repeats that was in the DNA when it was inherited. The cause of microsatellite instability may be a defect in the ability to repair mistakes made when DNA is copied in the cell.

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. The NCI coordinates the National Cancer Program, which conducts and supports research, training, health information dissemination, and other programs with respect to the cause, diagnosis, prevention, and treatment of cancer; rehabilitation from cancer; and the continuing care of cancer patients and their families.

National Institutes of Health (NIH) A federal agency in the U.S. that conducts biomedical research in its own laboratories; supports the research of nonfederal scientists in universities, medical schools, hospitals, and research institutions throughout the country and abroad; helps in the training of research investigators; and fosters communication of medical information.

Neuroblastoma A type of cancer that arises from immature nerve cells, most frequently those in the adrenal gland, but also those in the abdomen, chest, or near the spine. Neuroblastoma most often occurs in children younger than age 5.

Neuroendocrine tumors Rare types of cancer that form from cells that release hormones into the blood in response to a signal from the nervous system. Neuroendocrine tumors can occur anywhere in the body, although most frequently they arise in the lungs, appendix, small intestine, rectum, and pancreas.

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.

Osteoid osteoma A benign (noncancerous) bone tumor that usually develops in the long bones of the body, such as the femur (thighbone) and tibia (shinbone).

P

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

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.

Peptide A molecule that contains two or more amino acids, which are molecules that join together to form proteins.

Phase I/II clinical trial A study that tests the safety, side effects, and best dose of a new treatment. These clinical trials also test how well a certain type of cancer responds to a new treatment. In the phase II part of the clinical trial, patients usually receive the highest dose of treatment that did not cause harmful side effects in the phase I part of the clinical trial. Combining phases I and II may allow research questions to be answered more quickly or with fewer patients.

Phosphatidylinositol 3-kinases (PI3Ks) A family of proteins that work inside cells to send signals that direct numerous cellular functions, including cell growth, proliferation, and survival. The gene that encodes one component of one PI3K is mutated, resulting in an inappropriately active protein, in many types of cancer, including some breast cancers.

GLOSSARY

Platinum-based chemotherapy Treating cancer using chemotherapeutic agents that are coordination complexes of platinum. These drugs are used to treat almost 50 percent of cancer patients. Popular among these drugs are cisplatin and carboplatin, but several have been proposed or are under development.

Polyp A benign growth that protrudes from a mucous membrane, most typically associated with the colon.

Precision medicine In oncology, precision medicine refers to the tailoring of treatments to the individual characteristics—in particular, the genetics—of patients and their cancer.

Programmed death-1 (PD-1) A protein on the surface of immune cells called T cells. When PD-1 attaches to programmed death-ligand 1 (PD-L1) on other cells, it sends signals into the T cells to tell them to slow down and stop acting aggressively. Thus, PD-1 acts as an immune checkpoint protein or brake.

Programmed death-ligand 1 (PD-L1) A protein on the surface of many cell types, including some tumor cells. When it attaches to PD-1 on the surface of T cells, it sends signals into the T cells to tell them to slow down and stop acting aggressively.

Prostate cancer Cancer that starts in tissues of the prostate (a gland in the male reproductive system found below the bladder and in front of the rectum). In men, it is the most frequently diagnosed cancer and the second most common cause of death from cancer.

Prostate-specific antigen (PSA) A protein secreted by the prostate gland, increased levels of which are found in the blood of patients with cancer of the prostate.

Prostate-specific membrane antigen (PSMA) A protein that is usually found on the surface of normal prostate cells but is found in higher amounts on prostate cancer cells. PSMA may be used as a target in imaging to help find prostate cancer cells, especially those that may have come back or spread to other parts of the body.

Protein A molecule made up of amino acids that is needed for the body to function properly.

Psycho-oncology An interdisciplinary field to address the physical, psychological, social, and behavioral aspects of the cancer experience for both patients and caregivers.

Q

Quality of life The overall enjoyment of life. In cancer care, the term refers to an individual's sense of well-being and ability to carry out activities of daily living.

R

Radiation Energy released in the form of particle or electromagnetic waves. Common sources of radiation include radon gas, cosmic rays from outer space, medical X-rays, and energy given off by a radioisotope (unstable form of a chemical element that releases radiation as it breaks down and becomes more stable).

Radionuclide Also called radioisotope, a radionuclide is an unstable form of a chemical element that releases radiation as it breaks down and becomes more stable. In cancer medicine, radionuclides are used in diagnostic tests to detect the spread of cancer using imaging as well as in therapeutics, called radiopharmaceuticals, to treat cancer.

Radiotherapy The use of high-energy radiation from X-rays, gamma rays, neutrons, protons, and other sources to kill cancer cells and shrink tumors. Radiation may come from a machine outside the body (external-beam radiation therapy), or it may come from radioactive material placed in the body near cancer cells (internal radiation therapy). Systemic radiotherapy uses a radioactive substance, such as a radiolabeled monoclonal antibody, that travels in the blood to tissues throughout the body. Also called irradiation and radiation therapy.

Receptor A protein in a cell that attaches to specific molecules, such as hormones, from outside the cell, in a lock-and-key manner, producing a specific effect on the cell—for example, initiating cell proliferation. Receptors are most commonly found spanning the membrane surrounding a cell but can be located within cells.

Renal cell carcinoma The most common type of kidney cancer. It begins in the lining of the renal tubules in the kidney. Also called hypernephroma, renal cell adenocarcinoma, and renal cell cancer.

S

SARS-CoV-2 The virus that causes a respiratory disease called coronavirus disease 19 (COVID-19). SARS-CoV-2 is a member of a large family of viruses called coronaviruses.

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.

Standard of care The intervention or interventions generally provided for a certain type of patient, illness, or clinical circumstance. The intervention is typically supported by evidence and/or expert consensus as providing the best outcomes for the given circumstance.

Stereotactic body radiotherapy A type of radiation therapy that uses special equipment to position a patient and precisely deliver radiation to tumors in the body (except the brain). This type of radiation therapy helps spare normal tissue.

T

T cell A type of immune cell that protects the body from invading microorganisms and other foreign substances and that destroys infected and malignant cells. A T cell is a type of white blood cell. Also called T lymphocyte.

Treatment resistance The failure of cancer cells to respond to a treatment used to kill or weaken them. The cells may be resistant at the beginning of treatment or may become resistant after being exposed to the treatment.

Triple-negative breast cancer A type of breast cancer in which the cancer cells do not have estrogen receptors, progesterone receptors, or large amounts of HER2/neu protein. Also called ER-negative, PR-negative, HER2-negative breast cancer.

Tumor An abnormal mass of tissue that results when cells divide more than they should or do not die when they should. Tumors may be benign (not cancer) or malignant (cancer). Also called neoplasm.

Tumor microenvironment The cells, molecules, and blood vessels that surround and feed a cancer cell. A cancer can change its microenvironment, and the microenvironment can affect how a tumor grows and spreads.

U

Urothelial cancer The most common type of bladder cancer. It begins in urothelial cells that line the inside of the bladder. These cells can change shape and stretch when the bladder is full.

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.

APPENDIX

SUPPLEMENTAL TABLE 1

FDA-APPROVED THERAPEUTICS FOR CANCER RISK REDUCTION OR TREATMENT OF PRECANCEROUS CONDITIONS*

Cancer Risk Reduction		
Condition	**Generic Name**	**Trade Name**
Breast cancer	raloxifene	Evista
	tamoxifen	Nolvadex
Cervical, vulvar, vaginal, and anal cancers and dysplasia; genital warts	human papillomavirus quadrivalent vaccine (Types 6, 11, 16, and 18)	Gardasil
Cervical, head and neck, vulvar, vaginal, and anal cancers and dysplasia; genital warts	human papillomavirus 9-valent vaccine (Types 6, 11, 16, 18, 31, 33, 45, 52, and 58)	Gardasil 9
Cervical cancer and cervical dysplasia	human papillomavirus bivalent vaccine (Types 16 and 18)	Cervarix
Treatment of Precancerous Conditions		
Condition	**Generic Name**	**Trade Name**
Actinic keratosis	fluorouracil	Picato
	ingenol mebutate	Adricil
	diclofenac sodium	Voltaren
	5-aminolevulinic acid + photodynamic therapy (PDT)	
	masoprocol/nordihydroguaiaretic acid	Actinex
Bladder dysplasia	bacillus Calmette-Guerin (BCG)	
	valrubicin	Valstar
Esophageal dysplasia	porfimer sodium + photodynamic therapy (PDT)	Photofrin

*Adapted from Wu X, Patterson S, Hawk E. *Chemoprevention* – History and general principles. Best Practice Research Clinical Gastroenterology. 2011;25:445-59.

SUPPLEMENTAL TABLE 2

FDA-APPROVED THERAPEUTICS FOR THE TREATMENT OF CANCER

INCREASING PRECISION

DNA Synthesis Inhibitors (Antimetabolites)

Approved Indication	Generic Name	Trade Name
Multiple cancers	5-fluorouracil (5FU)	Adrucil
Certain leukemias	6-mercaptopurine	Purinethol
Breast and colorectal cancers	capecitabine	Xeloda
Certain leukemias; lymphoma	cladribine	Litrak; Movectro
Certain leukemias	clofarabine	Clolar
Certain leukemias; lymphoma	cytarabine	DepoCyt; Cytosar-U
Stomach cancer	floxuridine	FUDR
Certain leukemias; lymphoma	fludarabine	Fludara
Breast, lung, ovarian, and pancreatic cancers	gemcitabine	Gemzar
Certain leukemias	hydroxyurea	Droxia
Multiple cancers	methotrexate	Rheumatrex; Trexall
Multiple cancers	mitomycin	Mutamycin
Certain leukemias; lymphoma	nelarabine	Arranon
Lung and ovarian cancers; mesothelioma	pemetrexed	Alimta
Certain leukemias	pentostatin	Nipent
Certain lymphomas	pralatrexate	Folotyn

DNA-damaging Agents

Approved Indication	Generic Name	Trade Name
Ovarian cancer	altretamine	Hexalen
Certain leukemias	arsenic trioxide	Trisenox
Multiple cancers	bendamustine	Treanda
Certain lymphomas; squamous cell and testicular cancers	bleomycin sulfate	Blenoxane
Certain leukemias	busulfan	Myleran; Busulfex
Breast, lung, and ovarian cancers	carboplatin	Paraplatin; Paraplat
Brain tumors; certain lymphomas	carmustine	BiCNU
Multiple cancers	chlorambucil	Leukeran
Multiple cancers	cisplatin	Platinol-AQ
Multiple cancers	cyclophosphamide	Cytoxan
Melanoma; certain brain cancers	dacarbazine	DTIC-Dome
Multiple cancers	dactinomycin	Cosmegen
Certain leukemias	daunorubicin; daunomycin	Cerubidine
Multiple cancers	doxorubicin hydrochloride	Adriamycin PFS; Adriamycin RDF
Certain leukemias; breast and stomach cancers	epirubicin hydrochloride	Ellence
Testicular and lung cancers	etoposide phosphate	Etopophos; Topusar; VePesid
Certain type of leukemia	gemtuzumab ozogamicin	Mylotarg
Certain leukemias	idarubicin	Idamycin PFS
Multiple cancers	ifosfamide	Ifex
Certain types of leukemia	inotuzumab ozogamicin	Besponza
Colon, lung, and rectal cancers	irinotecan	Camptosar; Campostar
Pancreatic cancer	irinotecan liposome injection	Onivyde
Brain tumors	lomustine	CeeNU
Certain type of non-Hodgkin lymphoma	loncastuximab tesirine-lpyl	Zynlonta
Multiple cancers	mechlorethamine hydrochloride	Mustargen
Multiple cancers	melphalan	Alkeran
Multiple myeloma	melphalan flufenamide	Pepaxto
Certain lymphomas	methoxsalen	Uvadex
Multiple cancers	mitoxantrone	Novantrone
Colon cancer	oxaliplatin	Eloxatin
Testicular cancer	plicamycin	Mithracin
Certain lymphomas	procarbazine	Matulane
Pancreatic cancer	streptozocin	Zanosar
Melanoma; certain brain cancers	temozolomide	Temodar
Certain leukemias	thioguanine	Thioguanine Tabloid
Multiple cancers	thiotepa	Thioplex
Ovarian and small cell lung cancers	topotecan	Hycamtin
Colorectal cancer and stomach cancer	trifluridine and tipiracil	Lonsurf
Bladder cancer	valrubicin	Valstar

Cell Cytoskeleton-modifying Agents

Approved Indication	Generic Name	Trade Name
Multiple myeloma	belantamab mafodotin-blmf	Blenrep
Prostate cancer	cabazitaxel	Jevtana
Multiple cancers	docetaxel	Taxotere
Breast cancer; liposarcoma	eribulin mesylate	Halaven
Breast Cancer	ixabepilone	Ixempra
Multiple cancers	paclitaxel	Taxol
Breast, lung, and pancreatic cancers	paclitaxel albumin-bound particles	Abraxane
Certain type of non-Hodgkin lymphoma	polatuzumab vedotin-piiq	Polivy
Multiple cancers	vinblastine	Velban
Certain leukemias and lymphomas	vincristine	Oncovin
Certain leukemias and lymphomas	vincristine sulfate liposomes	Marqibo
Breast and lung cancers	vinorelbine tartrate	Navelbine

Antinutrients

Approved Indication	Generic Name	Trade Name
Certain leukemias	asparaginase	Elspar; Kidrolase
Certain leukemias	calaspargase pegol-mknl	Asparlas

Some drugs are available in multiple formulations; these have only been listed once. Where multiple trade names are used, only the most common have been listed.

FDA-APPROVED THERAPEUTICS FOR THE TREATMENT OF CANCER

INCREASING PRECISION

Gene Transcription Modifiers

Approved Indication	Generic Name	Trade Name
Certain lymphomas	bexarotene	Targretin
Liposarcoma and leiomyosarcoma	trabectedin	Yondelis
Certain leukemias	tretinoin (all-trans retinoic acid)	Vesanoid

Radiation-emitting Drugs

Approved Indication	Generic Name	Trade Name
Certain types of neuroendrocrine tumors	iobenguane I 131	Azedra
Certain types of neuroendocrine tumors	lutetium 177 dotatate	Lutathera
Prostate cancer bone metastases	radium Ra 223 dichloride	Xofigo

Cell Death-promoting Agents

Approved Indication	Generic Name	Trade Name
Certain form of leukemia	venetoclax	Venclexta

Hormones/Antihormones

Approved Indication	Generic Name	Trade Name
Prostate cancer	abarelix	Plenaxis
Prostate cancer	abiraterone acetate	Zytiga
Breast cancer	anastrozole	Arimidex
Prostate cancer	apalutamide	Erleada
Prostate cancer	bicalutamide	Casodex
Prostate cancer	darolutamide	Nubeqa
Prostate cancer	degarelix	Firmagon
Prostate cancer	enzalutamide	Xtandi
Prostate cancer	estramustine	Emcyt; Estracyt
Breast cancer	exemestane	Aromasin
Prostate cancer	flutamide	Eulexin
Metastatic breast cancer	fulvestrant	Faslodex
Prostate and breast cancers	goserelin acetate implant	Zoladex
Breast cancer	letrozole	Femara
Prostate cancer	leuprolide acetate	Eligard; Lupron; Viadur
Breast and endometrial cancers	megestrol acetate	Megace; Megace Oral Suspension
Certain type of prostate cancer	relugolix	Orgovyx
Breast cancer	tamoxifen	Nolvadex
Prostate cancer	triptorelin pamoate	Trelstar Depot

Immune System Modifiers

Approved Indication	Generic Name	Trade Name
Melanoma; kidney cancer	aldesleukin	Proleukin
Multiple cancers	interferon alfa-2b	Intron A
Myelodysplastic syndrome; certain lymphomas	lenalidomide	Revlimid
Kaposi Sarcoma; multiple myeloma	pomalidomide	Pomalyst

Proteasome Inhibitors

Approved Indication	Generic Name	Trade Name
Multiple myeloma	bortezomib	Velcade
Multiple myeloma	carfilzomib	Kyprolis
Multiple myeloma	ixazomib	Ninlaro

Protein Translation Inhibitors

Approved Indication	Generic Name	Trade Name
Certain type of leukemia	omacetaxine mepesuccinate	Synribo

Nuclear Export Inhibitors

Approved Indication	Generic Name	Trade Name
Certain type of lymphoma and multiple myeloma	selinexor	Xpovio

Epigenome-modifying Agents

Approved Indication	Generic Name	Trade Name
Myelodysplastic syndrome and certain type of leukemia	azacitidine	Vidaza
Certain lymphomas	belinostat	Beleodaq
Myelodysplastic syndrome	decitabine	Dacogen
Certain type of leukemia	enasidenib*	Idhifa
Certain type of leukemia	ivosidenib*	Tibsovo
Multiple myeloma	panobinostat	Farydak
Certain lymphomas	romidepsin	Istodax
Certain types of sarcoma and lymphoma*	tazemetostat	Tazverik
Certain lymphomas	vorinostat	Zolinza

DNA Repair Inhibitors

Approved Indication	Generic Name	Trade Name
Certain types of ovarian, fallopian tube, and primary peritoneal cancers	niraparib	Zejula
Certain forms of breast, ovarian, pancreatic, and prostate cancers	olaparib*	Lynparza
Certain types of ovarian and prostate cancer	rucaparib*	Rubraca
Certain type of breast cancer	talazoparib*	Talzenna

Immune Checkpoint Inhibitors

Approved Indication	Generic Name	Trade Name
Certain types of bladder, breast, and lung cancers	atezolizumab	Tecentriq
Certain types of bladder, kidney, and skin cancers	avelumab	Bavencio
Certain types of skin and lung cancer	cemiplimab-rwlc	Libtayo
Certain type of endometrial cancer	dostarlimab-gxly	Jemperli
Certain types of bladder cancer and lung cancer	durvalumab	Imfinzi

* includes companion diagnostic

Some drugs are available in multiple formulations; these have only been listed once. Where multiple trade names are used, only the most common have been listed.

FDA-APPROVED THERAPEUTICS FOR THE TREATMENT OF CANCER

INCREASING PRECISION

Immune Checkpoint Inhibitors *(continued)*

Approved Indication	Generic Name	Trade Name
Multiple cancers	ipilimumab	Yervoy
Multiple cancers	nivolumab	Opdivo
Multiple cancers	pembrolizumab	Keytruda

Bone-remodeling Inhibitors

Approved Indication	Generic Name	Trade Name
Potentially lethal complication of advanced cancers*	denosumab	Xgeva

Angiogenesis Inhibitors

Approved Indication	Generic Name	Trade Name
Kidney cancer	axitinib	Inlyta
Multiple cancers	bevacizumab	Avastin
Thyroid cancer; kidney cancer; liver cancer	cabozantinib	Cometriq; Cabometyx
Certain type of thyroid cancer; kidney cancer; liver cancer	lenvatinib	Lenvima
Kidney cancer; soft tissue sarcomas; gastrointestinal stromal tumors	pazopanib	Votrient
Certain types of lung, stomach, and liver cancers	ramucirumab	Cyramza
Colorectal cancer; gastrointestinal stromal tumors and liver cancer	regorafenib	Stivarga
Kidney cancer; certain type of thyroid cancer	sorafenib	Nexavar
Gastrointestinal stromal tumors; kidney cancer; some pancreatic cancers	sunitinib	Sutent
Certain type of kidney cancer	tivozanib	Fotivda
Thyroid cancer	vandetanib	Caprelsa
Colorectal cancer	ziv-aflibercept	Zaltrap

Cell Lysis Mediators

Approved Indication	Generic Name	Trade Name
Certain leukemias	alemtuzumab	Campath
Certain types of leukemia	blinatumomab	Blincyto
Certain lymphomas	brentuximab vedotin	Adcetris
Multiple myeloma	daratumumab	Darzalex
Neuroblastoma	dinutuximab	Unituxin
Multiple myeloma	elotuzumab	Empliciti
Certain lymphomas	ibritumomab	Zevalin
Multiple myeloma	isatuximab-irfc	Sarclisa
Certain type of breast cancer	margetuximab-cmkb	Margenza
Certain types of non-Hodgkin lymphoma	mogamulizumab-kpkc	Poteligeo
Certain type of leukemia	moxetumomab pasudotox-tdfk	Lumoxiti
Neuroblastoma	naxitamab-gqgk	Danyelza
Certain form of leukemia; certain form of lymphoma	obinutuzumab	Gazyva
Certain leukemias	ofatumumab	Arzerra
Certain lymphomas	rituximab	Rituxan
Certain type of non-Hodgkin lymphoma	tafasitamab-cxix	Monjuvi
Certain type of leukemia	tagraxofusp-erzs	Elzonris

Oncolytic Virus

Approved Indication	Generic Name	Trade Name
Melanoma	talimogene laherparepvec	Imlygic

Therapeutic Vaccine

Approved Indication	Generic Name	Trade Name
Prostate cancer	sipuleucel-T	Provenge

CAR T-cell Therapy

Approved Indication	Generic Name	Trade Name
Certain type of non-Hodgkin lymphoma	autoleucel brexucabtagene	Tecartus
Certain type of non-Hodgkin lymphoma	axicabtagene ciloleucel	Yescarta
Multiple myeloma	idecabtagene vicleucel	Abecma
Certain type of non-Hodgkin lymphoma	lisocabtagene maraleucel	Breyanzi
Certain types of leukemia and non-Hodgkin lymphoma	tisagenlecleucel	Kymriah

Cell-signaling inhibitors

Approved Indication	Generic Name	Trade Name
Certain types of breast cancer	abemaciclib	Verzenio
Certain types of leukemia and lymphoma*	acalabrutinib	Calquence
HER2+ breast cancer	ado-trastuzumab emtansine	Kadcyla
Certain type of lung cancer	afatinib	Gilotrif
Certain form of lung cancer	alectinib	Alecensa
Certain type of breast cancer	alpelisib*	Piqray
Certain type of lung cancer	amivantamab-vmjw	Rybrevant
Certain type of gastrointestinal stromal tumor and leukemia	avapritinib	Ayvakit
Certain type of leukemia	bosutinib	Bosulif
Certain type of melanoma	binimetinib and encorafenib	Braftovi and Mektovi
Certain type of lung cancer	brigatinib	Alunbrig
Certain type of lung cancer	capmatinib	Tabrecta

* includes companion diagnostic

Some drugs are available in multiple formulations; these have only been listed once. Where multiple trade names are used, only the most common have been listed.

FDA-APPROVED THERAPEUTICS FOR THE TREATMENT OF CANCER

INCREASING PRECISION

Cell-signaling inhibitors *(continued)*

Approved Indication	Generic Name	Trade Name
Certain type of metastatic ALK-positive lung cancer	ceritinib	Zykadia
Colon cancer*; head and neck cancer	cetuximab	Erbitux
Certain type of colorectal cancer*	cetuximab and encorafenib*	Erbitux and Braftovi
Certain form of melanoma*	cobimetinib	Cotellic and Zelboraf
Certain type of non-Hodgkin lymphoma	copanlisib	Aliqopa
Certain type of non-Hodgkin lymphoma and specific lung cancers*	crizotinib	Xalkori
Multiple cancers	dabrafenib	Tafinlar
Certain type of lung cancer	dacomitinib*	Vizimpro
Some leukemias	dasatinib	Sprycel
Certain types of leukemia and non-Hodgkin lymphoma	duvelisib	Copiktra
Certain type of bladder cancer	enfortumab vedotin-ejfv	Padcev
NTRK-positive solid tumors and certain lung cancers	entrectinib	Rozlytrek
Certain type of bladder cancer	erdafatinib*	Balversa
Certain type of breast and gastrointestinal cancer	fam-trastuzumab deruxtecan-nxki	Enhertu
Certain type of myeloproliferative neoplasm	fedratinib	Inrebic
Some lung cancers*; pancreatic cancer	erlotinib	Tarceva
Some pancreatic cancers; kidney cancer; noncancerous kidney tumors; HER2+ breast cancers; neuroendocrine tumors	everolimus	Afinitor
Lung cancer	gefitinib	Iressa
Certain type of leukemia	gilteritinib*	Xospata
Certain type of leukemia	glasdegib	Daurismo
Certain form of lymphoma and non-Hodgkin lymphoma	ibrutinib	Imbruvica
Certain types of leukemia and lymphoma	idelalisib	Zydelig
Some leukemias; stomach cancer; certain type of skin cancer	imatinib	Gleevec; Glivec
HER2+ breast cancers	lapatinib	Tykerb
NTRK-positive solid tumors	larotrectinib	Vitrakvi
Certain type of lung cancer	lorlatinib*	Lobrena
Certain types of leukemia	midostaurin*	Rydapt
Certain form of lung cancer	necitumumab	Portrazza
Certain type of breast cancer	neratinib	Nerlynx
Some leukemias	nilotinib	Tasigna
Soft tissue sarcoma	olaratumab	Lartruvo
Certain form of lung cancer*	osimertinib	Tagrisso
Certain subtype of breast cancer	palbociclib	Ibrance
Colon cancer	panitumumab	Vectibix
Certain type of bile duct cancer	pemigatinib*	Pemazyre
HER2+ breast cancer	pertuzumab	Perjeta
Tenosynovial giant cell tumor	pexidartinib	Turalio
Certain types of leukemia	ponatinib	Iclusig
Certain types of lung and thyroid cancers	pralsetinib	Gavreto
Certain type of breast cancer	ribociclib	Kisqali
Gastrointestinal stromal tumor	ripretinib	Qinlock
Myelofibrosis	ruxolitinib	Jakafi
Certain types of breast and bladder cancer	sacituzumab govitecan-hziy	Trodelvy
Certain types of lung and thyroid cancer	selpercatinib	Retemvo
Neurofibromatosis type 1	selumetinib	Koselugo
Most common type of skin cancer	sonidegib	Odomzo
Certain type of lung cancer	sotorasib	Lumakras
Kidney cancer	temsirolimus	Toricel; Torisel
Certain type of lung cancer	tepotinib	Tepmetko
Multiple cancers	trametinib	Mekinist
HER2+ breast cancer	trastuzumab	Herceptin
Certain type of breast cancer	tucatinib	Tukysa
Certain types of non-Hodgkin lymphoma	umbralisib	Ukoniq
Thyroid cancer	vandetanib	Caprelsa
Certain type of blood cancer and melanoma*	vemurafenib	Zelboraf
Most common type of skin cancer	vismodegib	Erivedge
Certain type of non-Hodgkin lymphoma	zanubrutinib	Brukinsa

* includes companion diagnostic

Some drugs are available in multiple formulations; these have only been listed once. Where multiple trade names are used, only the most common have been listed.

SUPPLEMENTAL TABLE 3

SURGICAL AND RADIOTHERAPY TREATMENTS FOR CANCER

Type of Surgical Procedure*	Description	Applicable Cancer
Mastectomy	Surgery to remove the entire breast	Breast cancer
Lumpectomy (or partial mastectomy)	Surgery to remove the cancer and some normal tissue around it, but not the breast itself	Breast cancer
Orchiectomy	Surgery to remove one or both testicles	Testicular cancer
Video-Assisted Thoracoscopic Surgery (VATS)	Surgery performed using a small video camera that is introduced into the patient's chest via small incisions	Multiple head, neck, and chest cancers
Laparoscopic surgery	Surgery done with the aid of a laparoscope	Variety of abdominal cancers
Reconstructive surgery	Surgery to restore the function or appearance of organs or tissues that were either removed or changed by cancer treatment	Breast and head and neck cancer
Limb-sparing surgeries	Surgery to remove a tumor in a limb (arm or leg) without removing the whole limb	Sarcoma and other cancers
Partial nephrectomy	Surgery to remove part of one kidney or a kidney tumor, but not an entire kidney	Kidney cancer
The Whipple/modified Whipple procedure	Surgery to remove head of the pancreas, the duodenum, a portion of the stomach, and other nearby tissues	Pancreatic cancer
Total mesorectal excision	Surgery to remove significant length of the bowel around a tumor	Rectal cancer
Nerve-sparing prostatectomy	Surgery to remove part or all of the prostate and some of the tissue around it	Prostate cancer
Transanal Endoscopic Microsurgery (TEM)	Surgery performed through the rectum with specially designed microsurgical instruments to remove rectal tumors and early stage rectal cancers	Rectal cancer
Modified retroperitoneal lymph node dissection	Surgery to remove abdominal lymph nodes	Testicular cancer
Sentinel lymph node biopsies	Surgery to identify, remove, and examine sentinel lymph node to determine whether cancer cells are present	Breast, melanoma, and colorectal cancers
Robotic or computer-assisted surgeries	Surgeries that use robotic systems to aid in procedures	Multiple cancers
Brachytherapy	A form of radiotherapy where a sealed radiation source is placed inside or next to the area requiring treatment	Cervical cancer, prostate cancer, ocular melanoma, breast cancer, skin cancer, recurrent cancers, other cancers
Three-dimensional conformal radiotherapy (3DCRT)	A type of radiation delivery that shapes the radiation beams to match the shape of the tumor	Multiple cancers
Intensity modulated radiotherapy (IMRT)	An advanced formed of 3DCRT that uses advanced computer programs to calculate and deliver precise radiation doses to a malignant tumor or specific areas within the tumor	Multiple cancers
Image-guided radiotherapy (IGRT)	The use of imaging during radiation therapy to improve the precision and accuracy of treatment delivery	Many cancers, especially those that may move during treatment or are located adjacent to critical organs

*Delivered alone or in combination with other types of radiation listed in the table with or without concurrent chemotherapy, targeted therapy, or hormonal therapy

SUPPLEMENTAL TABLE 3 *(continued)*

SURGICAL AND RADIOTHERAPY TREATMENTS FOR CANCER

Type of Surgical Procedure*	Description	Applicable Cancer
Stereotactic radiosurgery (SRS)	A type of external radiation therapy that uses special equipment to position the patient and advanced computer programs to calculate and deliver precisely a single large dose of radiation to a tumor	Brain metastases
Stereotactic body radiotherapy (SBRT) or Stereotactic ablative radiotherapy (SABR)	Administers very high doses of radiation in a few fractions (usually 5 or less), using several beams of various intensities aimed at different angles to precisely target the tumor anywhere in the body	Liver cancer, lung cancer, pancreatic cancer, spinal metastases, oligometastases, recurrent cancers requiring re-irradiation
Proton therapy	A type of radiation treatment that uses protons to treat cancer	Pediatric cancers, certain unresectable skull base or head and neck cancers, certain CNS tumors, ocular tumors, recurrent cancers requiring re-irradiation, hepatocellular carcinoma, certain retroperitoneal sarcoma**
Particle therapy	A form of external beam radiotherapy using beams of energetic protons, neutrons, or positive ions such as carbon ion for cancer treatment	Carbon ion therapy is being tested for several solid cancers outside of the U.S.
Neoadjuvant or adjuvant radiotherapy	Radiation is delivered either before (neoadjuvant) or after (adjuvant) surgery, sometimes with concurrent systemic therapy	Multiple cancers
Organ preservation approach	Definite radiotherapy +/- chemotherapy that is designed to produce cure while preserving the organ where the tumor is located	Certain head and neck cancers, breast cancer (with lumpectomy), anal cancer, esophageal cancer, bladder cancer

*Delivered alone or in combination with other types of radiation listed in the table with or without concurrent chemotherapy, targeted therapy, or hormonal therapy
**ASTRO group 1 guideline

SUPPLEMENTAL TABLE 4

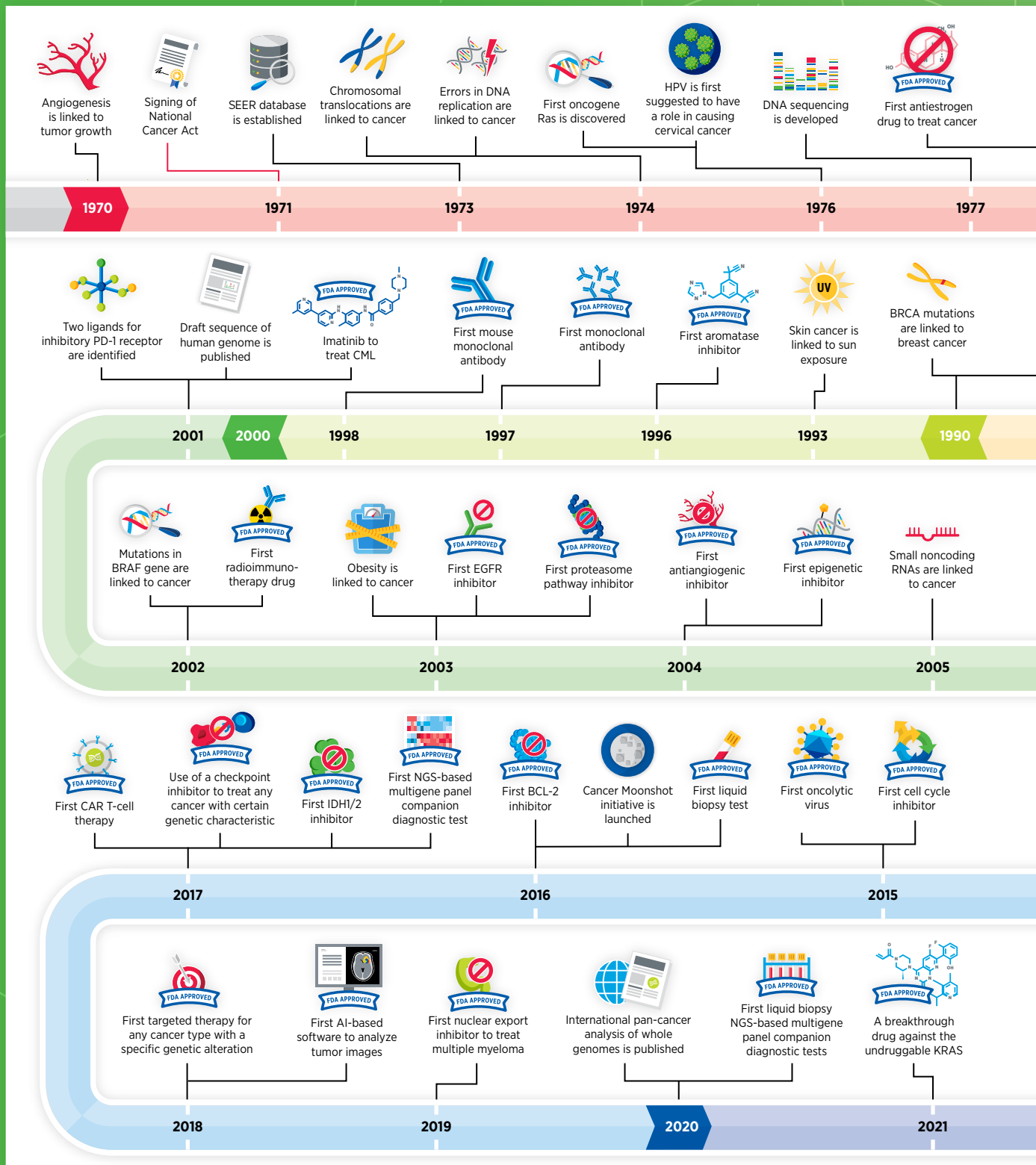
NEWLY FDA-APPROVED ANTICANCER THERAPEUTICS: AUGUST 1, 2020–JULY 31, 2021

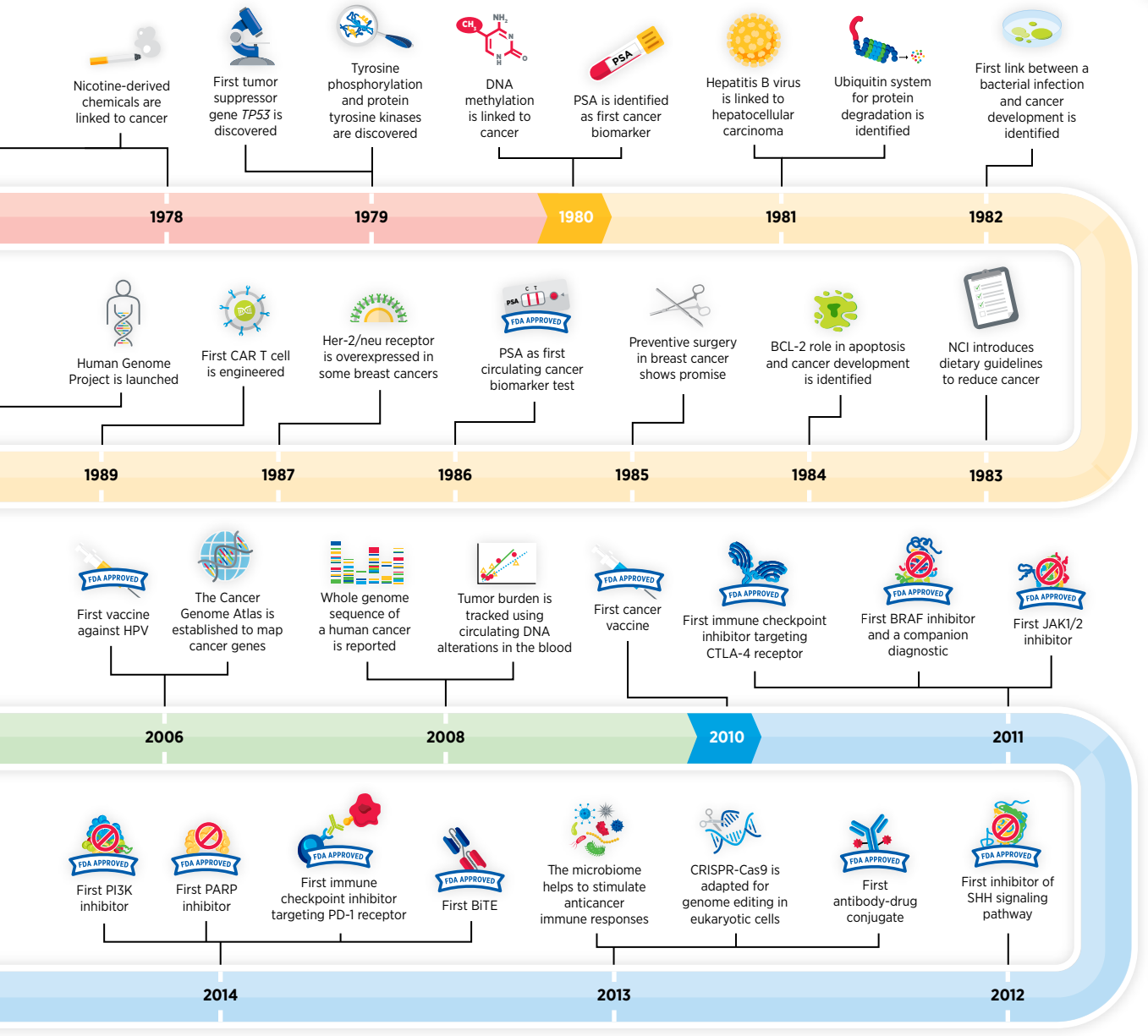
Approved Indication	Generic Name	Clinical Trial(s)
Angiogenesis Inhibitors		
Certain type of kidney cancer	tivozanib	NCT02627963
Cell-signaling Inhibitors		
Certain type of lung cancer	amivantamab-vmjw†	NCT02609776
Certain type of leukemia*	avapritinib	NCT02561988; NCT03580655
Certain type of non-Hodgkin lymphoma*	crizotinib†	NCT00939770
Bile duct cancer	infigratinib†	NCT02150967
Certain types of lung and thyroid cancers	pralsetinib†	NCT03037385
Certain type of lung cancer	sotorasib†	NCT03600883
Certain type of lung cancer	tepotinib	NCT02864992
Certain types of non-Hodgkin lymphoma	umbralisib	NCT02793583
Cell Cytoskeleton-modifying Agents		
Multiple myeloma	belantamab mafodotin-blmf	NCT03525678
DNA-damaging Agents		
Certain type of gastrointestinal cancers*	fam-trastuzumab deruxtecan-nxki	NCT03329690
Certain type of non-Hodgkin lymphoma	loncastuximab tesirine-lpyl	NCT03589469
Multiple myeloma	melphalan flufenamide	NCT02963493
Certain type of bladder cancer*	sacituzumab govitecan-hziy	NCT03547973
Epigenome-modifying Agents		
Certain type of leukemia*	azacitidine	NCT01757535
Hormones/Antihormones		
Certain type of prostate cancer	relugolix	NCT03085095
Immunotherapeutics		
Certain type of non-Hodgkin lymphoma*	axicabtagene ciloleucel	NCT03105336; NCT02348216
Certain type of skin and lung cancers*	cemiplimab-rwlc†	NCT03088540; NCT03132636
Certain type of endometrial cancer	dostarlimab-gxly†	NCT02715284
Multiple myeloma	idecabtagene vicleucel	NCT03361748
Mesothelioma*	ipilimumab and nivolumab	NCT02899299
Certain type of non-Hodgkin lymphoma	lisocabtagene maraleucel	NCT02631044
Certain type of breast cancer	margetuximab-cmkb	NCT02492711
Neuroblastoma	naxitamab-gqgk	NCT03363373; NCT01757626
Gastric and gastroesophageal junction cancers*	nivolumab	NCT02743494; NCT02872116
Certain types of breast, gastric, and gastroesophageal junction cancers*	pembrolizumab†	NCT02819518; NCT03189719; NCT03615326
Imaging Agents		
Certain type of neuroendocrine tumor	copper Cu 64 dotatate	NCT04334837
Prostate cancer	gallium 68 PSMA-11	NCT0336847; NCT02918357
Prostate cancer	piflufolastat F 18	NCT02981368; NCT03739684
Companion Diagnostic Tests		
Certain type of lung cancer	N/A	NA
Certain types of breast, lung, ovarian, and prostate cancers	N/A	NA
Surgery Guiding Devices		
Osteoid osteoma in the extremities	N/A	NCT02349971
Artificial intelligence-guided assessment for liver cancer	N/A	NCT03213314

*New cancer type approved 2020-2021
†Requires a companion diagnostic

SUPPLEMENTAL FIGURE 1

50 YEARS OF DISCOVERY SCIENCE DRIVING CLINICAL BREAKTHROUGHS





A timeline of selected major scientific discoveries and clinical breakthroughs in the quest to find cures for cancer. Also shown are FDA approvals of first-in-class revolutionary therapeutics. These anticancer treatments have helped save lives and have informed new and novel strategies to effectively treat a broad spectrum of cancer types. This report also highlights discoveries of key genes and pathways as well as development of breakthrough therapeutics against lung cancer (**Figure 4**, see p. 16). melanoma (**Figure 5**, see p. 17), and HPV-related cancers (**Figure 11**, see p. 52). Also highlighted elsewhere are milestones in developing the KRAS inhibitor sotorasib (**Figure 20**, see p. 96), angiogenesis inhibitors (**Figure 21**, see p. 98), and immune checkpoint inhibitors (**Figure 23**, see p. 109).

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