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The mission of the American Association for Cancer Research (AACR) is to prevent and cure cancer through research, education, communication, collaboration, science policy and advocacy, and funding for cancer research. Through its programs and services, the AACR fosters cutting edge research in cancer and related sciences; accelerates the dissemination of new research findings among scientists, clinicians, patient advocates, and others dedicated to the conquest of cancer; promotes science education and training; and advances the understanding of cancer etiology, prevention, detection, diagnosis, regulatory science, and treatment throughout the world.

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AACR CANCER PROGRESS REPORT 2020

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TURNING SCIENCE INTO LIFESAVING CARE

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ABOUT THE AMERICAN ASSOCIATION FOR CANCER RESEARCH

Founded in 1907, the American Association for Cancer Research (AACR) is the world's first and largest professional organization dedicated to advancing cancer research and its mission to prevent and cure cancer. AACR membership includes more than 47,000 laboratory, translational, and clinical researchers; population scientists; other health care professionals; and patient advocates residing in 127 countries. The AACR marshals the full spectrum of expertise of the cancer community to accelerate progress in the prevention, biology, detection, diagnosis, and treatment of cancer by annually convening more than 30 scientific conferences and educational workshops, the largest of which is the AACR Annual Meeting with more than 23,000 attendees. 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 across the spectrum of cancer science and medicine 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 the related sciences in saving lives from cancer. For more information about the AACR, visit **AACR.org.**

A MESSAGE FROM THE AACR

This is an uncertain time for everyone around the world, including those of us working in the field of cancer science and medicine and the patients and families who rely on us. There has been remarkable progress against cancer over the past few decades; in the United States overall cancer incidence and death rates are declining steadily and the number of children and adults who are surviving longer after a cancer diagnosis has been increasing. However, our ability to continue the current pace of progress is in jeopardy because of the enormous global public health challenge posed by the Coronavirus Disease 2019 (COVID-19) pandemic.

The *AACR Cancer Progress Report 2020* provides a comprehensive overview of the breakthroughs in cancer care that are being made because of medical research, much of which is supported by federal investments in the National Institutes of Health (NIH). As highlighted in the report, bipartisan leadership in Congress that has delivered five consecutive years of robust annual funding increases for the NIH has sparked a new wave of scientific discovery and technological innovation. This has increased our basic scientific understanding 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.

In the past year, we have brought a record number of scientific advances to patients with cancer in the form of new treatments for their particular diseases. Among the 20 new treatments that were approved by the U.S. Food and Drug Administration (FDA) in the 12 months covered in this report are 16 molecularly targeted therapeutics that are part of the precision medicine revolution in cancer care. The surge in the number of molecularly targeted therapeutics is being fueled by discoveries in the field of cancer genomics wrought by multidisciplinary teams of researchers. One caveat is that thus far, most cancer genomics data come from individuals of Western European ancestry. To ensure that precision medicine benefits every cancer patient, including individuals from racial and ethnic minorities and other underserved populations, it is imperative that we increase our knowledge of cancer genomics in these populations. Many of the steps needed to enhance diversity in cancer science and medicine, including in cancer genomics, are described in the inaugural AACR Cancer Disparities Progress Report, which was unveiled at a congressional briefing on September 16, 2020.

The rapid expansion in the use of checkpoint inhibitors, which are immunotherapeutics that work by releasing the brakes on natural cancer-fighting immune cells called T cells, is continuing unabated. Five of these transformative therapeutics were approved in the past 12 months for treating additional types of cancer, and one was approved for treating cancer based solely on the presence of a specific genetic biomarker rather than the site of origin. Facilitating the convergence of expertise from an increasingly diverse array of disciplines, such as mathematics, physics, chemistry, engineering, and computer science, will allow us to make even more pioneering advances in immunotherapy, providing new hope for many more patients with cancer.

Despite the significant progress we are making against cancer, there is a vital need for continued transformative research. This urgency is underscored by the sobering reality that cancer will claim more than one life every minute of every day in the United States this year. This number is predicted to grow considerably in the coming decades largely because of overall population growth and because of growth of the segment of the U.S. population age 65 and older—the population most at risk for cancer.

At the start of 2020, we were in a strong position to make major strides toward the goal of preventing and curing all types of cancer. Unfortunately, the global health crisis caused by the COVID-19 pandemic has impeded the positive momentum against cancer. There is grave concern that the delays in cancer screening, diagnosis, and treatment caused by the pandemic will have significant negative effects on outcomes for patients. There is particularly high concern for racial and ethnic minorities and other underserved populations because these groups already experience cancer health disparities and are now shouldering a disproportionate burden of COVID-19. Racial and ethnic disparities in COVID-19 as well as the recently witnessed inhumanities against people of color have refocused the nation's attention on stark inequities in health care, and it is critical for everyone to play a role in eradicating the social injustices that are barriers to health equity.

The COVID-19 pandemic has created many challenges for cancer research, with laboratories shuttered temporarily or refocused to work on COVID-19-related projects. While it is imperative that cancer researchers contribute their unique expertise to combat the unprecedented global pandemic, we must not forget that there are many patients with cancer who are urgently awaiting more effective treatment options.

Ensuring that medical research remains a priority for our nation's policy makers is absolutely essential if we are to maintain the momentum against cancer, fuel the economy, and help the United States to retain its important position as the global leader in medical research. Therefore, the AACR urges Congress to continue to support annual funding increases that are robust, sustained, and predictable for the NIH, NCI, FDA, and CDC. These actions will keep us on the path of making lifesaving progress for patients with cancer around the world.

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

Antoni Ribas, MD, PhD
Chair, AACR President 2020–2021
Professor of Medicine
Professor of Surgery
Professor of Molecular
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Los Angeles, California

EXECUTIVE SUMMARY

This is an unprecedented time in our history. In the cancer field, transformative research and technological innovation are driving astounding progress against the collection of diseases we call cancer. Unfortunately, our ability to continue the rapid pace of this progress is in jeopardy because of the enormous global public health challenge posed by the Coronavirus Disease 2019 (COVID-19) pandemic.

As the first and largest professional organization in the world dedicated to advancing every area of cancer research, the American Association for Cancer Research (AACR) is dedicated to increasing public understanding of cancer and the importance of medical research for saving lives. It is also committed to advocating for increased annual federal funding to government entities that fuel progress against cancer and improve public health, in particular the 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 tenth edition of the report highlights how research continues to extend and improve 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 science and medicine, as well as how unwavering, bipartisan support from Congress, in the form of robust and sustained annual increases in funding for the NIH, NCI, and FDA, is vital if we are to accelerate the pace of progress against cancer for the benefit of families everywhere.

"Since I began treating melanoma, I have seen firsthand the significant benefit that molecularly targeted therapy and immunotherapy have had for patients."

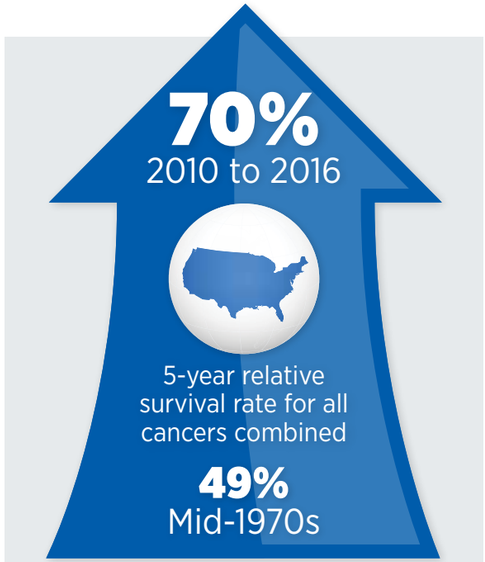
ANTONI RIBAS, MD, PhD
AACR PRESIDENT, 2020–2021

CANCER IN 2020

Research is the backbone of progress against cancer because it spurs the development of new and better approaches to preventing, detecting, diagnosing, treating, and curing some of the many diseases we call cancer. These advances are driving down overall U.S. cancer incidence and death rates and increasing the number of children and adults who are surviving longer after a cancer diagnosis. For example, the age-adjusted overall U.S. cancer death rate declined by 29 percent from 1991 to 2017, which is the last year for which these data are available. In addition, the U.S. 5-year relative survival rate for all cancers combined rose from 49 percent for people diagnosed in the mid-1970s to 70 percent for those diagnosed from 2010 to 2016.

Even though we are making significant progress, cancer continues to be an enormous public health challenge around the world. One challenge is that the number of new cancer cases is projected to increase dramatically in the coming decades, with the rise in the United States alone projected to be from just over 1.8 million in 2020 to more than 2.3 million in 2040. This sharp increase is anticipated largely because of 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, including African Americans and Hispanics, also are shouldering a disproportionate burden of the ongoing COVID-19 pandemic, laying bare stark inequities in health care. Disparities in health care are among the most significant forms of racial inequality and injustice, and it is imperative that all stakeholders play a role in eradicating the social injustices that are barriers to health equity, which is one of our most basic human rights.



The immense toll of cancer is felt through both the number of lives it affects each year and its economic impact. In the United States, cancer health care spending is estimated to have been $161.2 billion in 2017, the last year for which these data are available. This does not include the indirect costs of lost productivity due to cancer-related morbidity and death, which were $30.3 billion and $150.7 billion, respectively. With the personal and economic burden of cancer predicted to rise in the next few decades, it is vital that the nation invest 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, division, and 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 multiplication, others are acquired because of persistent exposure to substances that damage genetic material such as toxicants in tobacco smoke and ultraviolet radiation (UV) from the sun, and yet others are acquired as a result of chronic inflammation fueled by medical conditions such as Crohn's disease.

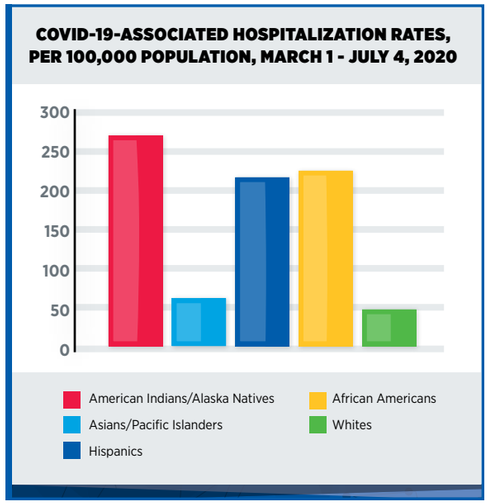
Although genetic mutations underpin cancer initiation and development in most cases, epigenetic abnormalities, as well as interactions between cancer cells and their environment—known as the tumor microenvironment—also play an important role.

SPECIAL FEATURE ON COVID-19 AND CANCER

The year 2020 will be inextricably linked to COVID-19, a disease that has drastically altered every facet of life, including cancer research and care. Therefore, this edition of the AACR Cancer Progress Report includes a special feature that provides an overview of the disease, the contribution of cancer research to its detection and treatment, and the opportunities and challenges ahead for the cancer community.

The global health crisis caused by the rapid spread of COVID-19 was declared a pandemic by the World Health Organization (WHO) on March 11, 2020. As of July 31, 2020, more than 4.5 million people in the United States had been diagnosed with COVID-19 and more than 150,000 people in the country had died from the disease. These figures were about 25 percent of the global numbers on that same day.

COVID-19 is caused by infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Not everyone who becomes infected with SARS-CoV-2 goes on to develop symptoms of COVID-19. Even among people who develop symptoms, there is a wide diversity in the severity of the disease. Older adults, males, and individuals of any age with certain underlying medical conditions are at an increased risk for severe COVID-19 illness.



The COVID-19 pandemic has created many challenges across the continuum of cancer care, with concern about the effects that delays in cancer screening, diagnosis, and treatment will have on outcomes for patients with cancer, in particular racial and ethnic minorities because these population groups have shouldered a disproportionate burden of COVID-19. Cancer researchers are playing a pivotal role in addressing the COVID-19 pandemic and are continuing to innovate to respond to the challenges posed by the pandemic, including adapting the conduct of clinical trials.

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 could 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, 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 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 morbidity and mortality in the United States. Thanks to such initiatives, cigarette smoking among U.S. adults has been declining steadily since 1965, when it was 42 percent, and reached an all-time low of 13.7 percent in 2018. However, the use of electronic cigarettes (e-cigarettes) is rapidly increasing among U.S. adolescents, youth, and young adults. New legislation that raises the federal minimum age of sale of all tobacco products, including e-cigarettes, to 21 years should accelerate progress against cigarette smoking and e-cigarette use among these populations, but more must be done to curb their access to tobacco products.

The prevalence of obesity, another major risk factor for cancer, which is linked to 15 types of cancer, continues to rise among U.S. children and adults. In the past two decades, obesity rates among children, adolescents, and young adults ages 2 to 19 have risen from 13.9 percent to 19.3 percent. During the same period, obesity rates among adults age 20 and older increased from 30.5 percent to 42.4 percent.

Therefore, it is essential that all stakeholders work together to enhance the dissemination of our current knowledge of cancer prevention and implement evidence-based policies to minimize the morbidity and mortality of cancers attributable to preventable causes.

SCREENING FOR EARLY DETECTION

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 treated successfully.

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. 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 screen large segments of the U.S. 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 personal 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.

TURNING SCIENCE INTO LIFESAVING CARE

The dedicated efforts of individuals working throughout the cycle of medical research are constantly powering the translation of new research discoveries, made as a result of innovative cancer science, into lifesaving advances for people in the United States and around the world.

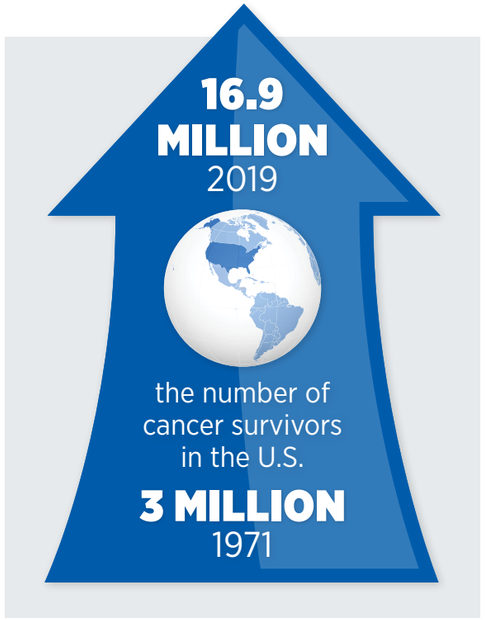
Among the advances made from August 1, 2019, to July 31, 2020, are the 20 new therapeutics that were approved by the FDA for treating patients with various types of cancer. During the same period, the uses of 15 previously approved anticancer therapeutics were expanded by the FDA to include the treatment of additional types of cancer.

Sixteen of the new anticancer therapeutics target specific molecules involved in cancer and are referred to as molecularly targeted therapeutics. They are part of the precision medicine revolution in cancer care that is improving the lives of patients such as six-year old **Camden Green,** whose brain tumor was found to be fueled by a genetic alteration that matched her to the molecularly targeted therapeutic entrectinib (Rozlytrek), and **Sandra Griego,** who has a rare type of cancer called epithelioid sarcoma, which is susceptible to the molecularly targeted therapeutic tazemetostat (Tazverik) (pp. 80 and 94, respectively).

Five of the previously approved anticancer therapeutics that were approved for treating additional types of cancer are immunotherapeutics called checkpoint inhibitors. With these new approvals, as of July 31, 2020, one or more checkpoint inhibitors have been approved for treating 16 types of cancer and for treating any type of solid tumor characterized by the presence of certain molecular characteristics, microsatellite instability–high, DNA mismatch–repair deficiency, and tumor mutational burden–high. These transformative treatments yield remarkable and durable responses for many patients, as highlighted in the report by the experiences of **Dr. Al Stroberg** and **Leonard Ganz** (pp. 98 and 102, respectively).

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 with just 3 million in 1971.



Despite the progress, survivors of cancer often 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, but one in four survivors reports a poor physical quality of life and one in 10 reports a poor mental health–related quality of life. Adopting a healthy lifestyle, using palliative care, and psycho-oncology programs can improve quality of life.

The transition from initial cancer treatment to follow-up, long-term survivorship care can be complicated. Emerging evidence suggests that survivors of cancer receive the highest level of care if their care is well coordinated, either by an oncologist and primary care physician, by multiple specialists, or by an oncogeneralist—a primary care physician with specific expertise in caring for patients and survivors with cancer. However, we need to identify the optimal way to provide comprehensive, coordinated care to all survivors of cancer.

LOOKING TO THE FUTURE

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

As we look to the future, many researchers, including **AACR President, 2020–2021, Antoni Ribas, MD, PhD,** (p. 120), are confident that we will be able to overcome the global public health crisis caused by COVID-19 and continue working diligently to accelerate progress against cancer by increasing collaboration and harnessing the new wave of technological innovation. For example, innovation in the application of artificial intelligence approaches such as machine learning to the analysis of vast amounts of health care information will accelerate the pace of progress across the breadth of cancer science and medicine. Cutting-edge techniques such as gene editing using CRISPR/Cas are poised to transform the development of cell therapies. The incorporation of novel technologies such as liquid biopsies into the clinic has the potential to have a major positive impact on early detection, diagnosis, and treatment of cancer in the near future.

COMBATTING CANCER THROUGH SCIENCE-BASED, PATIENT-CENTERED POLICIES

Federal investment in the NIH, NCI, FDA, and CDC has 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 improve public health.

If we are to continue to accelerate the pace of progress against cancer, we need robust, sustained, and predictable annual budget increases for the NIH and NCI. We also need continued congressional commitment to supporting the FDA and the cancer prevention and control programs at the CDC. These vital investments will help support a diverse 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

Medical research is driving scientific and technological innovation that is spurring progress against the many diseases we call cancer. Thanks to remarkable bipartisan efforts in Congress the NIH budget has grown significantly in the past five years, allowing our nation's researchers to capitalize on many of the unprecedented scientific opportunities that exist today to improve health and save lives.

In addition to making medical research a national priority, Congress has acknowledged the need for increased innovation at the FDA to ensure the rapid translation of research discoveries into safe and effective treatments, and swift dissemination of these treatments to patients who need them urgently. Furthermore, Congress recognizes the vital role of an active CDC to protect our citizens from serious health threats.

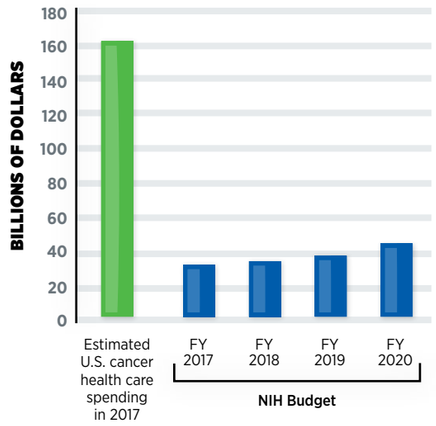
During this unprecedented time in our nation's history, there is also a need for our nation's leaders to take on a much bigger role in confronting and combatting the structural and systemic racism that contributes to health disparities. Renewed attention has been drawn to the issue of pervasive racism and social injustices in light of the COVID-19 pandemic as well as the recent atrocities against people of color. Likewise, it is time for the scientific community to step up, and partner with Congress to assess and address this issue within the research community.

THEREFORE, THE AACR URGES CONGRESS TO:

- Continue to support robust, sustained, and predictable growth for the NIH and NCI by providing increases in their FY2021 base budgets of at least $3 billion and $522 million, respectively, for a total funding level of $44.7 billion for the NIH and $6.9 billion for the NCI.
- Ensure that the $195 million in funding designated through the 21st Century Cures Act for targeted initiatives, including the National Cancer Moonshot, is fully appropriated in FY2021 and is supplemental to the overall increase in the NIH base budget.
- Support the FDA's critical regulatory science initiatives by providing an increase of at least $120 million in discretionary budget authority in FY 2021.
- Support the 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.
- Continue to support appropriation bills that include increased funding for CDC's Office of Smoking and Health, to continue to strengthen comprehensive tobacco prevention and control programs.
- Provide $50 million for the second year of the Childhood Cancer Data Initiative and "no less than" $25 million for the continued implementation of the Childhood Cancer STAR Act.
- Exempt NIH and other key public health agencies from the highly restrictive FY 2021 budget caps to allow them to forcefully respond to the COVID-19 health crisis, as well as to support the science that is necessary to improve and save lives from the myriad of diseases faced by Americans and by people all over the world.

DIRECT COSTS OF CANCER CARE ARE STARTLING

The cost of treating cancer stands in stark contrast to the NIH budget.

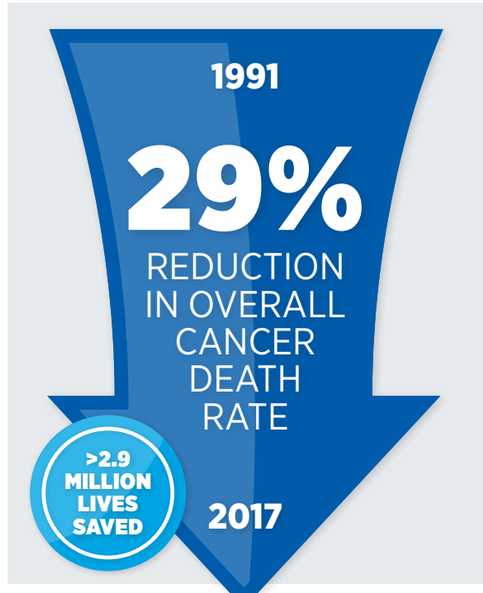


- Eliminate the pervasive racial biases in the conduct of cancer research that have led to significant inequities in cancer care, low participation for minorities in clinical trials, and an underrepresentation of racial and ethnic minority scientists in the cancer research workforce by supporting a congressional effort that calls on the National Academies of Science, Engineering, and Medicine to undertake a study to assess systemic racism in academia.

The COVID-19 pandemic is one of the greatest health crises that this country has ever faced, leading to thousands of lives lost, an economy thrown into chaos, and significant alterations in everyday life for millions of Americans. The pandemic has also highlighted the vital importance of medical research. Across the country, funding for ongoing medical research was diverted to stop the spread of COVID-19 and to expeditiously develop vaccines and treatments for this unprecedented disease.

In the face of the current health crisis due to the COVID-19 pandemic, cancer and other diseases continue to be major ongoing challenges. If we hope to reach the day when cancer is no longer a major health threat to our nation's citizens, Congress must provide the critical funding that is essential for research supported by the NIH and NCI. By providing robust, sustained, and predictable annual funding increases for the NIH and NCI in FY 2021 and beyond, Congress will accelerate the pace at which we make future scientific advances, capitalize on prior investments in cancer research, spur innovation and economic prosperity for our country, and bring lifesaving cures to many patients in the United States and around the world.

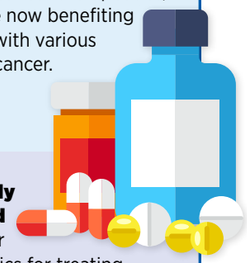
A SNAPSHOT OF A YEAR IN PROGRESS



BETWEEN AUGUST 1, 2019 AND JULY 31, 2020, THE FDA APPROVED:

20 **New** anticancer therapeutics, which are now benefiting patients with various types of cancer.

15 **Previously approved** anticancer therapeutics for treating new types of cancer.



RESEARCH CONTINUES TO DRIVE ADVANCES IN CANCER TREATMENT, LEADING TO:

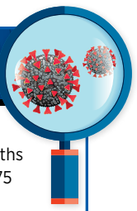
the first treatment specifically for patients with a rare soft tissue cancer called epithelioid sarcoma, such as **Sandra Griego,** p. 94.

a new therapeutic to target NTRK and ROS1, which is providing new hope to children like **Camden Green,** p. 80, and adults with a wide array of cancer types.

the first targeted therapeutics to treat patients with pancreatic and prostate cancers based on the presence of BRCA or HRD mutations.

the first checkpoint inhibitor to treat patients who have the TMB-h biomarker in their tumor, such as **Leonard Ganz,** p. 102, and **Barbara Bigelow,** p. 103.

COVID-19 AND CANCER



As of July 31, 2020, there were 17,622,478 confirmed cases of COVID-19 and 680,165 deaths from the disease globally; there were 4,566,275 cases and 153,391 deaths in the United States.

Cancer researchers are uniquely positioned to respond to many of the challenges posed by COVID-19 and have lent their expertise in numerous ways to address the pandemic.

The COVID-19 pandemic has significantly disrupted cancer care, with concerns that the delays that have occurred in screening, diagnosis, and treatment will cause thousands of additional deaths from cancer in the future and exacerbate cancer health disparities.

The COVID-19 pandemic interrupted many aspects of cancer research, including clinical trials; remarkable changes to the conduct of clinical trials, many of which address long-standing challenges, have been proposed and/or implemented.

CANCER IN 2020

IN THIS SECTION YOU WILL LEARN:

- In the United States, the overall cancer death rate has been steadily decreasing since the 1990s, with the reductions from 1991 to 2017 translating into more than 2.9 million cancer deaths avoided.
- The decline in the overall cancer death rate is being fueled in large part by a dramatic decrease in the lung cancer death rate predominantly as a result of reduced smoking rates.
- Since the 1990s, the age-adjusted overall cancer death rate has decreased more rapidly among African Americans than among whites; however, the African American population still disproportionately shoulders the burden of overall cancer mortality.
- The economic burden of cancer is enormous, both in the United States and globally.

RESEARCH: DRIVING PROGRESS AGAINST CANCER

Research continues to be our best defense against cancer because it is the driving force behind all clinical and policy advances that improve cancer prevention, detection, diagnosis, treatment, and, increasingly, cures for individuals around the world.

Each advance that spurs progress against cancer is the result of many years of collaboration between different stakeholders dedicated to fundamentally changing the face of this devastating disease (see sidebar on **Driving Progress against Cancer Together,** p. 9).

In the United States, the remarkable progress being made against cancer is illustrated by the fact that more children, adolescents, and adults are surviving longer after a cancer diagnosis. The U.S. 5-year relative survival rate for all cancers combined rose from 49 percent for people diagnosed in the mid-1970s to 70 percent for those diagnosed from 2010 to 2016 (2). The 5-year relative survival rate for all cancers diagnosed among U.S. children and adolescents (ages 0–19) from 2010 to 2016 was 85 percent, up from 63 percent for those diagnosed in the mid-1970s (2)(3) (see **Figure 1**, p. 10).

Another sign of the extraordinary progress being made against cancer in the United States is that the age-adjusted overall cancer death rate has been declining since 1991 (5). The largest reduction in the U.S. age-adjusted overall cancer death rate ever seen in a single year, 2.2 percent, occurred from 2016 to 2017, which is the last year for which these data are available. Overall, since its peak in 1991, the rate has declined by 29 percent, a reduction that translates into more than 2.9 million cancer deaths avoided.

The decline in the U.S. age-adjusted overall cancer death rate has been fueled in large part by a dramatic decline in the lung cancer death rate predominantly as a result of reduced smoking rates (5). The decline in the lung cancer death rate has accelerated in recent years, falling 2.4 percent each year from 2008 to 2013 and then falling 4.3 percent each year from 2013 to 2017. During the 2013 to 2017 period, the death rate for melanoma, which is the deadliest type of skin cancer, also fell at a remarkable rate of 6.4 percent each year (5). This striking reduction has been attributed in large part to the innovative new therapeutics approved by the U.S. Food and Drug Administration (FDA) for treating certain patients with the disease since 2011 (see **Figure 2,** p. 11).

As more and more new anticancer therapeutics are approved by the FDA and we continue to make scientific, clinical, and policy advances in cancer prevention, etiology, detection, diagnosis, treatment, and survivorship, we will accelerate the pace of progress against cancer. In this report, we focus on advances made during the 12 months from August 1, 2019, to July 31, 2020. Among the advances in cancer treatment that occurred during this period are the 20 new anticancer therapeutics approved by the FDA for introduction into the clinic. In addition, during this period, the FDA expanded the uses of 15 previously approved anticancer therapeutics to include additional types of cancer (see **Progress across the Spectrum of Cancer Treatment,** p. 69).

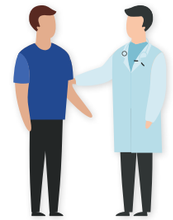
CANCER: AN ONGOING PUBLIC HEALTH CHALLENGE

Although we have made incredible progress against cancer, this disease continues to be an enormous public health challenge around the world (see sidebar on **Cancer: A Global Public Health Challenge,** p. 12). In 2020, making further inroads against cancer has been further complicated by

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 breakthroughs in the future. The key stakeholders are:

patients, survivors, and their caregivers, family members, and friends;



policy makers;

health care providers;

regulators;

academic and government researchers from a diverse array of specialties;

philanthropic organizations, cancer research organizations, and cancer-focused foundations;

biotechnology, pharmaceutical, diagnostics, and medical device companies;

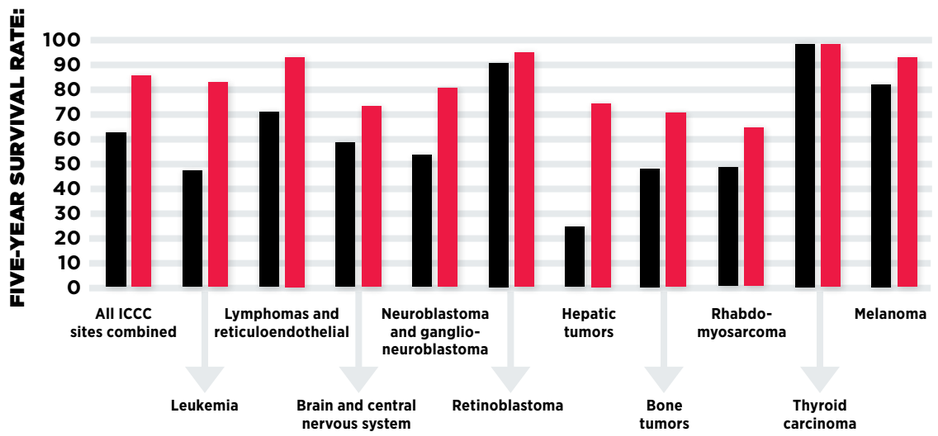
federal funding organizations; and

individual citizen advocates and members of advocacy groups;

health insurance payers.

Adapted from (1)

FIGURE 1 MAKING PROGRESS AGAINST CHILDHOOD CANCER



Five-year relative survival rates for U.S. children and adolescents (ages 0–19) diagnosed with cancer from 2010 to 2016 (red bars) were markedly higher than those for U.S. children and adolescents diagnosed from 1975 to 1979 (black bars). Cancers in children and adolescents are classified using the International Classification of Childhood Cancers (ICCC) (4). 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 (3)(2).

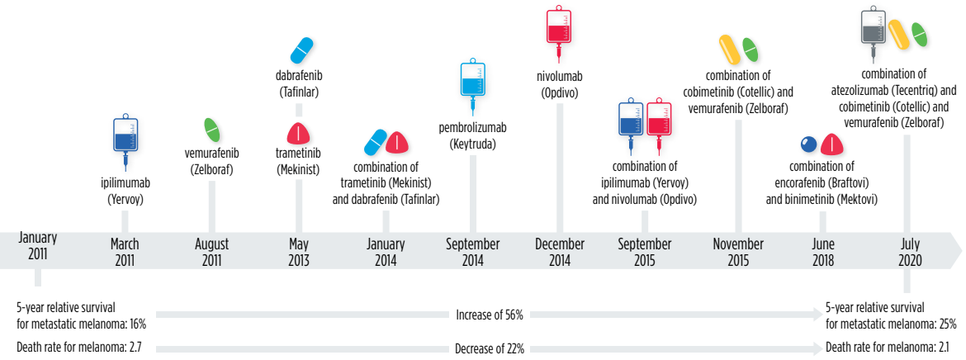
the Coronavirus Disease 2019 (COVID-19) pandemic, as discussed in **Special Feature on COVID-19 and Cancer** (p. 27). As one example, it is estimated that there will be at least 10,000 additional deaths from breast cancer and colorectal cancer over the next decade in the United States as a result of the adverse effect of the COVID-19 pandemic on screening and treatment for these two types of cancer (10).

The public health challenge posed by cancer in the United States is illustrated by the fact that researchers project that there will be 1,806,590 new cases of cancer diagnosed in 2020 and that there will be 606,520 deaths from the disease (8) (see **Table 1,** p. 13). These numbers translate into 206 new cancer cases and 69 cancer deaths every hour of every day.

Variable Progress among Types of Cancer, Subtypes of Cancer, and Stages of Diagnosis

Among the challenges we face is that progress against cancer has not been uniform for all types of cancer (2). Nor has it been uniform for all subtypes and stages of a given type of cancer (2). These challenges are illustrated by the fact that the 5-year relative survival rates for U.S. patients vary widely depending on the type of cancer diagnosed, the subtype of the cancer diagnosed, and the stage at diagnosis (2). For example, the overall 5-year relative survival rates of 98 percent for men with prostate cancer and 85 percent for adults with chronic lymphocytic leukemia (CLL) stand in stark contrast to the overall 5-year relative survival rates of 18 percent for people with liver cancer and 25 percent for those with acute myeloid leukemia (AML). Among women with breast cancer, those diagnosed with the triple-negative subtype have a 5-year relative survival rate of 77 percent, while those with the hormone receptor-positive subtype have a 5-year relative survival rate of greater than 90 percent. Substantial variation in the 5-year relative survival rate is also seen for the two main subtypes of lung cancer; it is 24 percent among patients with non-small cell lung cancer (NSCLC) and 6 percent among those with small cell lung cancer. In addition, among women with endometrial cancer and adults with colorectal cancer, those whose cancer is confined to the uterus, or to the colon or rectum, have 5-year relative survival rates of

FIGURE 2 INCREASING INNOVATIVE TREATMENT OPTIONS FOR MELANOMA



Melanoma is the deadliest form of skin cancer. On January 1, 2011, only 16 percent of patients with metastatic disease survived 5 or more years after diagnosis. At that time, 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 (6). From January 1, 2011, to July 31, 2020, 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), pembrolizumab (Keytruda), and nivolumab (Opdivo). In addition, the agency has 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 vemurafenib (Zelboraf), dabrafenib (Tafinlar), trametinib (Mekinist), cobimetinib (Cotellic), encorafenib (Braftovi), and binimetinib (Mektovi). 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 (6). Together, these innovative new therapeutics have helped increase the 5-year relative survival rate for metastatic melanoma by 56 percent and decrease the death rate by 22 percent. Researchers believe these improvements will continue as it was recently reported that overall survival at five years for patients treated with a combination of ipilimumab and nivolumab was 52 percent (7). Note: 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 (see Supplemental Table 2).

Data from (2)(8)(9).

95 percent and 90 percent, respectively, while those whose cancer has metastasized have 5-year relative survival rates of 17 percent and 14 percent, respectively.

Developing new and effective tests for the early detection of more types of cancer could help address the challenge of variable progress between types of cancer because patients diagnosed when cancer is at an early stage, before it has spread to other parts of the body, have a much higher likelihood of long-term survival than those diagnosed when the disease has spread to distant sites, an occurrence known as metastasis.

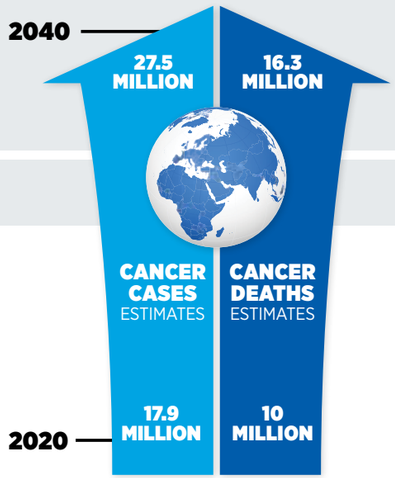
Disparities in Progress for Certain Population Groups

Cancer health disparities are another pressing challenge posed by cancer, as highlighted in the *AACR Cancer Disparities Progress Report 2020* (14).

The National Cancer Institute (NCI) defines cancer health disparities as adverse differences in cancer measures such as number of new cases, number of deaths, cancer-related health complications, survivorship and quality of life after

CANCER: A GLOBAL PUBLIC HEALTH CHALLENGE

Cancer is a leading cause of morbidity and mortality around the world. In 2018, the last year for which these data are available, it accounted for 16 percent of deaths worldwide (11).



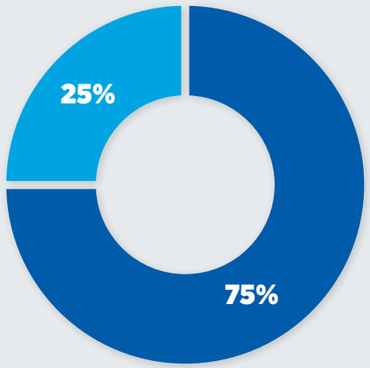
Overall Global Cancer Burden

The devastating impact of cancer is predicted to grow significantly in the coming decades unless new and more effective approaches to cancer prevention, early detection, and treatment are developed and effectively implemented (12). The projected increase in the overall global burden of cancer will largely be fueled by overall population growth and an expansion in the segment of the world's population most likely to develop cancer, those age 65 and older.

Global Childhood Cancer Burden

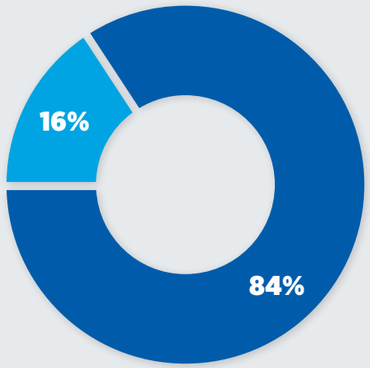
In 2020, it is estimated that 413,000 children ages 0 to 14 will develop cancer and 328,000 children will die from the disease (13). If access to health care is not markedly improved, in particular in low and lower middle income countries, it is anticipated that a total of 13.7 million cases of childhood cancer and 11.1 million deaths from childhood cancer will occur from 2020 to 2050. Most of these cases and deaths will be in low- and lower middle income countries. Investment to enable comprehensive scale-up of health care interventions has the potential to prevent about 6.2 million of the deaths from cancer in children from 2020 to 2050.

Cases of Childhood Cancer



Low and Lower Middle Income Countries

Deaths from Childhood Cancer



High and Higher Middle Income Countries

TABLE 1 ESTIMATED INCIDENCE AND MORTALITY FOR SELECTED CANCERS*

	Estimated 2019 Incidence			Estimated 2019 Deaths		
	Total	Male	Female	Total	Male	Female
All Sites	**1,762,450**	**870,970**	**891,480**	**606,880**	**321,670**	**285,210**
Head and Thorax Region						
Brain & other nervous system	23,890	13,590	10,300	18,020	10,190	7,830
Eye & orbit	3,400	1,890	1,510	390	210	180
Tongue	17,660	12,960	4,700	2,830	1,980	850
Mouth	14,320	8,430	5,890	2,660	1,690	970
Pharynx	17,950	14,630	3,320	3,640	2,820	820
Other oral cavity	3,330	2,360	970	1,620	1,270	350
Larynx	12,370	9,820	2,550	3,750	3,000	750
Lung & bronchus	228,820	116,300	112,520	135,720	72,500	63,220
Breast	279,100	2,620	276,480	42,690	520	42,170
Gastrointestinal (GI) System						
Esophagus	18,440	14,350	4,090	16,170	13,100	3,070
Stomach	27,600	16,980	10,620	11,010	6,650	4,360
Liver & intrahepatic bile duct	42,810	30,170	12,640	30,160	20,020	10,140
Gallbladder & other biliary	11,980	5,600	6,380	4,090	1,700	2,390
Pancreas	57,600	30,400	27,200	47,050	24,640	22,410
Small intestine	11,110	6,000	5,110	1,700	940	760
Colon and rectum	147950	78300	69650	53,200	28,630	24,570
Anus, anal canal, & anorectum	8,590	2,690	5,900	1,350	540	810
Urogenital System						
Kidney & renal pelvis	73,750	45,520	28,230	14,830	9,860	4,970
Ovary	21,750		21,750	13,940		13,940
Penis and other genital organs, male	2,200	2,200		440	440	
Prostate	191,930	191,930		33,330	33,330	
Testis	9,610	9,610		440	440	
Uterine cervix	13,800		13,800	4,290		4,290
Uterine corpus	65,620		65,620	12,590		12,590
Urinary bladder	81,400	62,100	19,300	17,980	13,050	4,930
Vulva	6,120		6,120	1,350		1,350
Vagina and other genital organs, female	6,230		6,230	1,450		1,450
Skin (Excluding Basal & Squamous)						
Melanoma-skin	100,350	60,190	40,160	6,850	4,610	2,240
Other nonepithelial skin	8,070	5,160	2,910	4,630	3,420	1,210
Hematological System						
Acute lymphocytic leukemia	6,150	3,470	2,680	1,520	860	660
Chronic lymphocytic leukemia	21,040	12,930	8,110	4,060	2,330	1,730
Acute myeloid leukemia	19,940	11,090	8,850	11,180	6,470	4,710
Chronic myeloid leukemia	8,450	4,970	3,480	1,130	670	460
Other leukemia	4,950	3,010	1,940	5,210	3,090	2,120
Hodgkin lymphoma	8,480	4,690	3,790	970	570	400
Non-Hodgkin lymphoma	77,240	42,380	34,860	19,940	11,460	8,480
Myeloma	32,270	17,530	14,740	12,830	7,190	5,640
Other Cancers						
Bones and joints	3,500	2,030	1,470	1,660	960	700
Soft tissue (including heart)	12,750	7,240	5,510	5,270	2,840	2,430

* Rounded to the nearest 10.

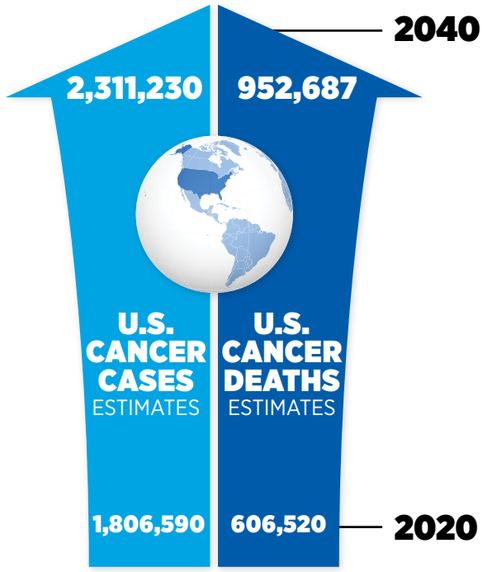
Source: Estimated new cases are based on 2001-2015 incidence rates reported by the North American Association of Central Cancer Registries (NAACCR). Estimated deaths are based on 2002-2016 US mortality data, National Center for Health Statistics, Centers for Disease Control and Prevention.

cancer treatment, screening rates, and stage at diagnosis that exist among certain population groups (15) (see sidebar on **U.S. Cancer Health Disparities,** p. 15).

Cancer health disparities are experienced by many segments of the U.S. population (see sidebar on **Which U.S. Population Groups Experience Cancer Health Disparities?** p. 16). The African American population is one group that has long shouldered a disproportionate burden of cancer (5)(18)(20). For example, in 1993, the overall cancer death rate for African American adults was 33 percent higher than it was for white adults. Encouragingly, this disparity had narrowed to 17 percent by 2017, the last year for which these data are available, because the overall cancer death rate decreased more rapidly among African American adults than it did among white adults from 1993 to 2017. Another sign of progress toward eliminating disparities in outcomes between African Americans and whites is that there was a greater increase in 5-year cancer survival for African Americans compared with whites from 2011 to 2014 (21). As a result, the disparity in 5-year cancer survival for African Americans compared with whites narrowed from 8.2 percent to 7.7 percent during that period. Despite the progress, the burden of overall cancer mortality is still significantly higher among African Americans compared with whites (5)(18)(20)(21).

Racial and ethnic minorities, including African Americans, not only shoulder a disproportionate burden of cancer, but also are shouldering a disproportionate burden of the ongoing COVID-19 pandemic, further highlighting stark inequities in health care. Disparities in health care are among the most significant forms of racial inequality and injustice, and it is imperative that everyone plays a role in eradicating the social injustices that are barriers to health equity, which is one of our most basic human rights.

Identifying, quantifying, and understanding the causes of health disparities, including cancer health disparities, is a vital step toward developing and implementing strategies to eliminate these disparities. Current knowledge of the complex and interrelated factors that contribute to cancer health disparities is discussed in detail in the *AACR Cancer Disparities Progress Report 2020* (14) (see sidebar on **Why Do U.S. Cancer Health Disparities Exist?** p. 17). For racial and ethnic minorities, adverse differences in many, if not all, of these factors are directly influenced by structural and systemic racism. New insights obtained through research, including basic research using samples from all U.S. population groups, through the participation of individuals from all these groups in clinical trials, and through increased collaboration among all stakeholders will allow us to make major strides toward eliminating cancer for all.



The Growing Population Burden of Cancer

The public health challenge posed by cancer will grow considerably in the United States and around the world in the coming decades unless we develop and effectively implement improved strategies for cancer prevention, early detection, and treatment (12) (see sidebar on **Cancer: A Global Public Health Challenge,** p. 12).

In the United States, it is predicted that the number of new cancer cases and the number of cancer deaths will rise to more than 2.3 million and almost 1 million, respectively, in 2040 (12). These sharp increases over the current numbers are anticipated largely because of overall population growth and because the segment of the U.S. population that accounts for most cancer diagnoses—those age 65 and older (2)—is expected to grow from 56 million in 2020 to 81 million in 2040 (22).

Cancer is primarily a disease of aging. In the United States, the median age at diagnosis is 66, and 54 percent of cancer cases are diagnosed in people age 65 and older (2). Progress is being made in reducing the overall U.S. cancer incidence rate, with the most recent data showing that it fell 0.6 percent each year from 2012 to 2016 (23). However, incidence rates for some types of cancer are increasing among people age 49 and younger at an alarming rate (24)(25). For example, the colorectal cancer incidence rate among people age 49 and younger increased 2.2 percent each year from 2012 to 2016 (24). This rise in early-onset colorectal cancer was driven

U.S. CANCER HEALTH DISPARITIES

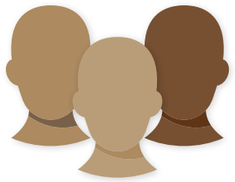
Adverse differences in numerous measures of cancer burden exist among certain population groups in the United States (see sidebar on **Which U.S. Population Groups Experience Cancer Health Disparities? p. 16**). Some recently identified examples of disparities in cancer incidence, mortality, and outcome are highlighted here. Disparities in other cancer measures are outlined elsewhere in the report (see sidebars on **Disparities in the Burden of Avoidable Cancer Risk Factors, p. 39; Disparities in Cancer Screening, p. 66; Disparities in Clinical Trial Participation, p. 73; Disparities in Cancer Treatment, p. 76;** and **Disparities in Quality of Life after a Cancer Diagnosis, p. 113).**

MORE THAN **50%**	Non-Hispanic Black children and adolescents who have cancer are **more than 50 percent** more likely to die from the cancer than non-Hispanic white children and adolescents who have cancer (16).
ALMOST **DOUBLE**	Hispanic adults have a stomach cancer death rate that is **almost double** that for non-Hispanic white adults (2).
TWICE AS LIKELY	American Indian/Alaska Native adults are **twice as likely** to develop liver and intrahepatic bile duct cancer as non-Hispanic white adults (5).
MORE THAN **DOUBLE**	Women living in Arkansas have a cervical cancer incidence rate that is **more than twice** that for women living in Vermont (5).
LESS THAN **HALF**	Patients with localized hepatocellular carcinoma, the most common type of liver cancer, who have no health insurance have overall survival that is **less than half** as long as those who have private health insurance (8 months versus 18 months) (17).
42% HIGHER	Men living in the poorest counties in the United States have a lung cancer death rate that is **42 percent higher** than that for men living in the most affluent counties (18).
70% MORE LIKELY	Bisexual women are **70 percent more likely** to be diagnosed with cancer than heterosexual women (19).

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

According to the National Cancer Institute, cancer health disparities in the United States are adverse differences in cancer measures such as number of new cases, number of deaths, cancer-related health complications, survivorship and quality of life after cancer treatment, screening rates, and stage at diagnosis that exist among certain population groups (15) including:

racial and ethnic minority groups;



individuals who lack or have limited health insurance coverage;

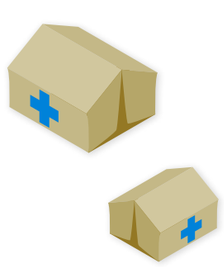
immigrants;

individuals with disabilities;

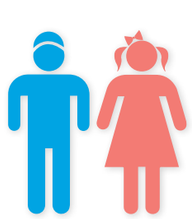
individuals of different ancestry

residents in certain geographic locations, including rural areas;

refugees or asylum seekers;

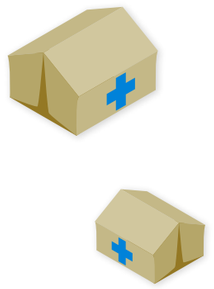


adolescents and young adults; and



individuals of low socioeconomic status;

members of the lesbian, gay, bisexual, and transgender community;



the elderly.

Adapted from (1)

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 may include, but are not limited to, differences or inequalities in:

Social Factors:
- Education
- Income
- Employment
- Health literacy

Psychological Factors:
- Stress
- Mental health

Clinical Factors:
- Access to health care
- Quality of health care

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

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

Genetic and biological factors

Cultural Factors:
- Cultural beliefs
- Cultural health beliefs

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

Adapted from (14)

largely by an increase in the colorectal cancer incidence rate among non-Hispanic whites. During the same period, the colorectal cancer incidence rate among those age 65 and older fell 3.3 percent each year. Similar trends have been seen for prostate cancer (25). For both examples, younger people were more likely to be diagnosed when the cancer had spread to distant sites, data that are being considered as colorectal cancer screening guidelines are reviewed (see sidebar on **Consensus Cancer Screening Recommendations for Average-risk Individuals,** p. 62).

CANCER: A COSTLY DISEASE. RESEARCH: A VITAL INVESTMENT

The enormous toll of cancer is felt not only through the number of lives it affects each year, but also through its immense economic impact.

In the United States, it is estimated that cancer health care spending was $161.2 billion in 2017, the last year for which these data are available (26). This does not include the indirect costs of lost productivity due to cancer-related morbidity and death, which were $30.3 billion and $150.7 billion, respectively. Overall, these numbers translate to about 1.8 percent of the country's gross domestic product.

The economic burden of cancer stands in stark contrast to the amount of money the federal government invests across all areas of medical research. In 2017, the same year that cancer health care spending was $161.2 billion, the budget for the National Institutes of Health (NIH), which is the largest medical research agency in the world, was just $34.15 billion, of which $5.64 billion went to the NCI.

If the number of cancer cases diagnosed each year in the United States increases in the coming decades as anticipated, the direct and indirect costs will also escalate (27).

The increasing personal and economic burden of cancer highlights the vital need for more transformative research to accelerate the pace of progress. Recent advances, some of which are highlighted in this report, were made as a result of the cumulative efforts of researchers from a diverse array of specialties. Their work is supported in large part by funds from the federal government that are administered through the NIH. The consecutive multibillion dollar increases for the NIH budget from fiscal year (FY) 2016 to FY2020 have helped researchers keep up with the pace of scientific innovation (see **Medical Research: A Wise Investment for America,** p. 129). It is imperative, however, that Congress continue to provide sustained, robust, and predictable increases in investments in the NIH and the NCI, as well as other federal agencies that are vital for fueling progress against cancer such as the FDA and the Centers for Disease Control and Prevention (CDC), in the years ahead (see **The AACR Call to Action,** p. 139).

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; the mutations are inherited in about 10 percent of cancer cases.
- 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.
- The more we know about the contributions of the numerous individual factors and their interplay in influencing cancer development among all populations, the more precisely and effectively we can prevent and treat cancer.

The extraordinary progress made against cancer as evidenced by the declining overall cancer death rate and the increasing number of survivors is a result of discoveries across the spectrum of cancer research from basic science to translational, clinical, and population research, which have deepened our understanding of how cancers arise and progress (see sidebar on **What Is Basic Research and How Does It Drive Progress against Cancer?** p. 20).

We now understand that cancer is 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 network, and form secondary tumors at remote sites.

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 that are packaged into condensed structures called chromosomes contained within a cell's nucleus (see sidebar on **Genetic and Epigenetic Control of Cell Function,** p. 21). 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.

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. 22). 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 heterogeneity, is an important part of a cancer's characteristics and fuels the cancer's ability to grow faster, escape therapy, evade the immune system, and metastasize to other organs. While inherited genetic mutations play a role in about 10 percent of all cancer cases (see **Table 2,** p. 23), 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. 21). Ongoing research continues to uncover new insights into the genetic basis of cancer (see sidebar on **Unraveling the Complexities of Cancer Genomics,** p. 24).

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 cancer, detect and/or intercept it early, and treat progressive disease. In general, the further a cancer has progressed, the harder it

WHAT IS BASIC RESEARCH AND HOW DOES IT DRIVE PROGRESS AGAINST CANCER?

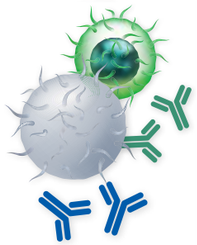
The National Institutes of Health (NIH) defines basic research as "the systematic study directed toward fuller knowledge or understanding of the fundamental aspects of a phenomenon and of observable facts without specific applications toward processes or products in mind." Basic research, however, has 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 (28). NIH-supported basic research projects significantly contribute to novel target identification and drug development (29).

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

Discovery of DNA and its 3-dimensional structure paved the way for understanding genetic mutations, the underlying basis of most cancers.

Basic research on normal cellular DNA repair elucidated how abnormalities in repair mechanisms can contribute to cancer development and led to the FDA approval of targeted therapies for breast, ovarian, pancreatic, and prostate cancer treatment (see **Expanding the Uses for PARP-targeted Therapeutics, p. 83**).

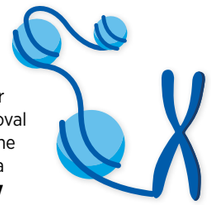
Decades of basic research in immunology underpinned the development of immunotherapeutics that have revolutionized the field of cancer treatment (see **Figure 17, p 101**).



Understanding the basic biology of NTRK genes and the discovery that NTRK gene fusions fuel the growth of several types of cancer laid the foundation for the development and FDA approval of the molecularly targeted therapeutics larotrectinib and entrectinib (see **Targeting an Array of Cancers That Share the Same Genetic Alteration, p. 79**).

Basic research into the immune system of bacteria led to the development of CRISPR technology; its utility to characterize and treat cancer is currently being investigated.

Research that led to the identification of epigenetic mechanisms underlying cancer cell multiplication was critical for the development and FDA approval of tazemetostat (Tazverik), for the treatment of epithelioid sarcoma (see **Using Epigenetic Therapy to Treat Cancer, p. 90**).



Adapted from (30)

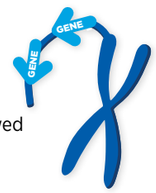
is to stop the chain of events that leads to the emergence of metastatic disease, which is the cause of most deaths from solid tumors (see **Screening for Early Detection,** p. 56).

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. 21). 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 (41). In contrast to genetic mutations, epigenetic changes are often reversible, providing an opportunity for therapeutic intervention. Our understanding of the role of epigenetics in cancer is, however,

GENETIC AND EPIGENETIC CONTROL OF CELL FUNCTION

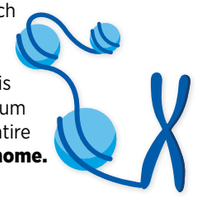
The genetic material of a cell comprises strings of **deoxyribonucleic acid (DNA),** a complex molecule comprised of four units called bases.

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),** followed by the various proteins the cell needs to function.



The entirety of a person's DNA is called the **genome.** Almost every cell in the body contains a 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 to produce the proteins that ultimately define the **function of the cell and the tissue** in which the cell resides.

Adapted from (1)

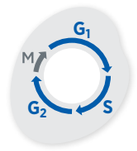
SOURCES OF GENETIC MUTATIONS

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:

About 10 percent of all new U.S. cancer cases are linked to inherited genetic mutations, which are present in each cell of the body from birth.

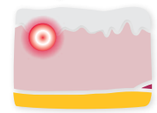
Most mutations, however, are acquired during a person's lifetime.

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



- Some occur because of persistent exposure to substances that damage genetic material, such as toxicants in tobacco smoke and ultraviolet radiation from the sun (see **Figure 6, p. 38**).

- Other mutations occur as a result of chronic inflammation fueled by medical conditions such as Crohn's disease (39).



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 (40)

GENETIC MUTATIONS

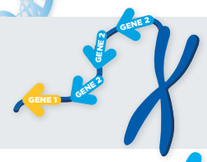
Types of genetic mutation known to lead to cancer include:

Single base changes

Deletion or insertion 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 variation

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 (1)

still incomplete, and continued research is needed to fulfil the real potential of the epigenome in cancer science and medicine. For example, according to a recent study, epigenetic alterations are associated with the development of certain forms of a rare cancer called gastrointestinal stromal tumors (GISTs) (42). More specifically, epigenetic marks called DNA methylation can displace certain anchors from the DNA. Loss of such anchors can lead to the activation of "on switches" in cancer-causing genes leading to tumor development.

Research aimed at the identification of genetic and epigenetic alterations that drive cancer development has led to the development of a new class of therapeutics—molecularly targeted therapeutics—which aim to rectify the cellular changes that arise due to such alterations. While these advances have revolutionized cancer treatment, they have also brought attention to the fact that individuals of European ancestry are grossly overrepresented in most clinical research investigations (43)(44). The lack of racial and ethnic diversity in human 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* (14).

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	*MYH*
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

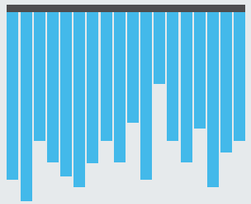
Source: http://www.cancer.gov/about-cancer/causes-prevention/genetics/risk-assessment-pdq and https://rarediseases.info.nih.gov/diseases/diseases-by-category/1/rare-cancers

UNRAVELING THE COMPLEXITIES OF CANCER GENOMICS

Global efforts from an international team of researchers have led to one of the most comprehensive studies of the whole genome of more than 2,600 tumors from 38 different types of cancer (31). Among the most important findings, published recently, 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 of such "driver" mutations (32). Interestingly, some of these mutations were detected in parts of the DNA referred to as "noncoding regions" which have traditionally not been a focus of cancer research (33). These discoveries are a major stride toward cataloging important cancer-causing genetic changes, which is critical for the advancement of precision medicine (see **Figure 3, p. 26**).

Unique patterns of mutations referred to as "mutational signatures" are often associated with processes 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 (see **Figure 6, p. 38**). Collectively, the researchers identified 97 signatures from a variety of tumors (34) (35). Notably, the causes of many such signatures were unknown, suggesting that more work needs to be done to identify currently unrecognized cancer risk factors.



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 (36). These findings have potentially important implications for early detection and interception of these cancers.

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.

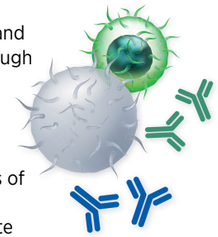
The tumor microenvironment is a specialized niche surrounding the cancer cells in a tumor and consists of immune cells—components of one's natural defense mechanism—as well as other cellular and molecular elements (see sidebar on **Cancer Growth: Local and Global Influences,** p. 25). Bidirectional communications between cancer cells and their microenvironment affect tumor growth and metastasis (45)(46). For instance, recent studies show that an important function of the local microenvironment is to provide sources of energy that promote multiplication and/or survival of metastatic cancer cells in an otherwise unfavorable environment (47)(48)(49). The tumor microenvironment can also shelter cancer cells from the effects of radiation, chemotherapy, and immunotherapy, thereby rendering them resistant to treatment (50).

Future studies that uncover additional cellular and molecular properties of the tumor microenvironment will be vital for improving cancer diagnosis and treatment. In this regard, a series of recent reports characterized the

CANCER GROWTH: LOCAL AND GLOBAL 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.



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

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

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

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

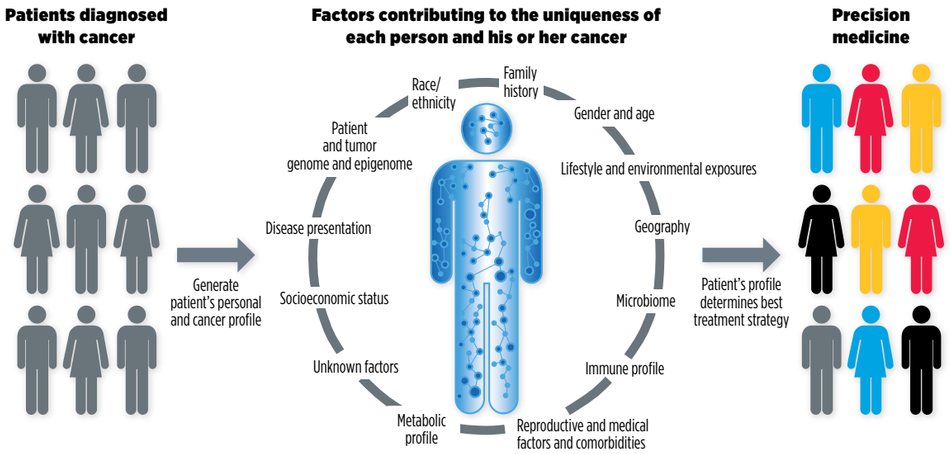
Adapted from (57)

cellular and molecular landscape of lung cancer cells and associated immune and other tumor-supporting cells in the microenvironment, across different regions in the tumor and over time (51). The data provide deep insights into the mechanisms by which the immune microenvironment interacts with lung cancer cells and vice versa in different regions within a tumor and across different tumors in a patient (52)(53). Furthermore, the studies characterize the wide range of dynamic alterations including mutations within immune and cancer cells that enables lung cancers to evade attack and elimination by the immune system (54)(55)(56). These discoveries have critical implications in understanding cancer progression and relapse, as well as response to state-of-the-art treatments such as immunotherapies.

CANCER DEVELOPMENT: INTEGRATING OUR KNOWLEDGE

Over the past decade, we have made significant progress in how we understand and treat 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. Therefore, each person's cancer is unique, and 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 3,** p. 26). The aim of precision medicine is to use information about a person's genes, proteins, and environment to prevent, diagnose, and treat disease.

FIGURE 3 PRECISION MEDICINE



Precision medicine is broadly defined as treating patients based on characteristics that distinguish them from other patients 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, exposures, lifestyle, microbiome, and other comorbidities. Currently, genomics is the predominant factor influencing precision medicine, but as we learn more about the additional factors, we can 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 such profiling improves outcomes for individuals.

Precision medicine aims to use genetic and other information about a patient's tumor, as well as other factors, to help diagnose, plan treatment, determine how well treatment is working, or make a prognosis, with the overarching goal of improving clinical outcomes and minimizing unnecessary diagnostic and therapeutic interventions. While genomics is the predominant factor currently guiding this approach, adoption of precision medicine has already shown substantial benefits in survival in patients with cancer (58)(59). Precision medicine holds tremendous potential in cancer science and medicine, given that we are experiencing a rapid evolution of state-of-the-art technologies that are enabling researchers to uncover additional key players in cancer development, such as novel tumor genomics, immune system, energy metabolism, lifestyle, and environmental exposures, at an unprecedented pace. An area of active focus is the accumulation of relevant data from racial and ethnic minorities, the lack of which really minimizes the current implementation of precision medicine for these populations (60). Going forward, concerted efforts from all stakeholders in medical research will be critical in order to deliver the full potential of precision medicine to the entire cancer community.

SPECIAL FEATURE ON COVID-19 AND CANCER

IN THIS SECTION YOU WILL LEARN:

- As of July 31, 2020, there were 17,622,478 confirmed cases of Coronavirus Disease 2019 (COVID-19) and 680,165 deaths from the disease globally; there were 4,566,275 cases and 153,391 deaths in the United States.
- Older adults, males, and individuals of any age with certain underlying medical conditions are at an increased risk for severe COVID-19 illness.
- Racial and ethnic minorities have been disproportionately impacted by COVID-19 for many of the same reasons that they shoulder a disproportionate burden of cancer.
- The COVID-19 pandemic has disrupted cancer care for many people, causing concerns that the delays in screening, diagnosis, and treatment will cause thousands of additional deaths from cancer in the future.
- Cancer researchers are uniquely positioned to respond to many of the challenges posed by COVID-19.

The year 2020 will be inextricably linked to Coronavirus Disease 2019 (COVID-19), the disease that had affected more than 17.6 million people worldwide and taken more than 680,000 lives by July 31, 2020 (61).

At the end of 2019 a disease presenting as pneumonia with unknown origins was identified in Wuhan, a city in the Hubei Province of China (62). In early January 2020, the cause of the disease was identified as a novel coronavirus by the Chinese Center for Disease Control and Prevention. The International Committee on Taxonomy of Viruses termed the virus severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and in February 2020, the World Health Organization (WHO) designated the disease caused by SARS-CoV-2 as Coronavirus Disease 2019, or COVID-19. The ensuing global health crisis, which was declared a pandemic by the WHO on March 11, 2020, continues to exact an immense toll on people and countries around the world.

This Special Feature on COVID-19 and Cancer will provide an overview of the basic biology of SARS-CoV-2, the epidemiology of COVID-19, the influence of cancer research on the detection and treatment of the disease, and the opportunities and challenges ahead for the cancer community due to the COVID-19 pandemic.

UNDERSTANDING THE BIOLOGY OF SARS-COV-2 INFECTION AND COVID-19

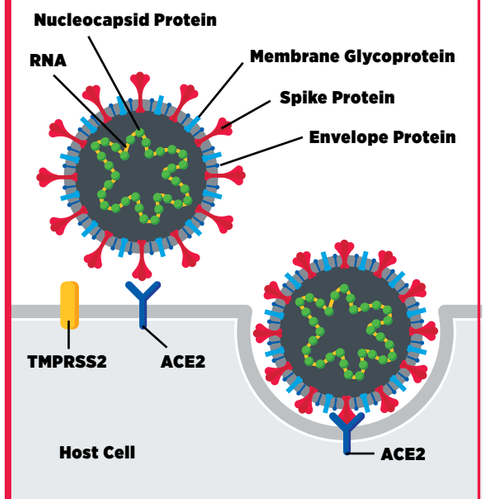
Named because of their crown-like appearance, coronaviruses constitute a family of hundreds of viruses most commonly found in birds and small mammals (for example, bats and rodents), but occasionally in humans. There are seven coronaviruses, including SARS-CoV-2, that are known to infect humans; four result in cold-like illnesses while the other three are responsible for the deadly, global outbreaks of the respiratory illnesses severe acute respiratory syndrome (SARS), Middle East respiratory syndrome (MERS), and COVID-19.

Viruses generally cannot live very long outside a host organism. They have no means of independent reproduction or metabolism and are composed primarily of genetic material, either DNA or RNA, encased in a protein "shell" called a capsid or nucleocapsid. The capsid may or may not be enclosed in an envelope; most viruses that infect animals, including SARS-CoV-2, have this envelope.

To multiply, a virus must attach to and enter an appropriate host cell, where it hijacks the host's genetic material and cellular machinery to produce viral genomes and capsid and envelope proteins. These capsids are assembled around new genomes and transported to the host cell surface where they meet up with new envelope proteins and exit the host in a process called budding.

SARS-CoV-2 uses RNA as its genetic material and has four major structural proteins: the spike, nucleocapsid, membrane, and envelope proteins (63) (see **Figure 4,** p. 28). To infect a human, the spike protein attaches to a protein called angiotensin-converting enzyme 2 (ACE2), which is found on the surface of certain human cells in the nasal passages, lungs, and gastrointestinal tract (64).

FIGURE 4
HOW SARS-COV-2 ENTERS A CELL



Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the virus that causes Coronavirus Disease 2019 (COVID-19). SARS-CoV-2 particles are spherical and enter cells that have a protein called angiotensin-converting enzyme 2 (ACE2) on the surface. Each SARS-CoV-2 particle contains RNA encased in a "shell" formed of the nucleocapsid protein. This is enclosed in a lipid envelope. Three structural proteins pass through the lipid envelope, the envelope protein, the membrane protein, and the spike protein. The spike protein attaches to ACE2, which is found on the surface of certain human cells including some of those lining the nasal passages and lungs. To enter these cells, the virus needs another protein, called TMPRSS2, to be present on the cells. TMPRSS2 modifies the spike protein, triggering fusion of the SARS-CoV-2 lipid envelope with host lipid membranes. This allows the encased RNA to fully enter the cell where, after it is uncoated from the nucleocapsid protein, it hijacks the host's genetic material and cellular machinery to produce copies of itself and to produce more envelope, nucleocapsid, membrane, and spike proteins.

To enter these cells, the virus needs another protein, called TMPRSS2, to be present on the cells. TMPRSS2 is naturally found in several tissues of the human body including the prostate, lung, gastrointestinal tract, and urinary tract, and it is frequently found together with ACE2 on cells in the nasal passages and lungs.

Once infected with SARS-CoV-2, individuals can begin shedding and transmitting virus particles within two to three days, often before experiencing disease symptoms (65). For most people, it takes about four to five days after infection with SARS-CoV-2 for symptoms to appear, but for others it can take up to 14 days (66). Among the symptoms of COVID-19 are fever, dry cough, loss of taste and/or smell, fatigue, muscle pain/body aches, and difficulty breathing. As the disease progresses, moving from the upper to lower respiratory tract and throughout the body, the disease can cause damage to nearly every organ and system in the body (67)(68) (see **Figure 5,** p. 29).

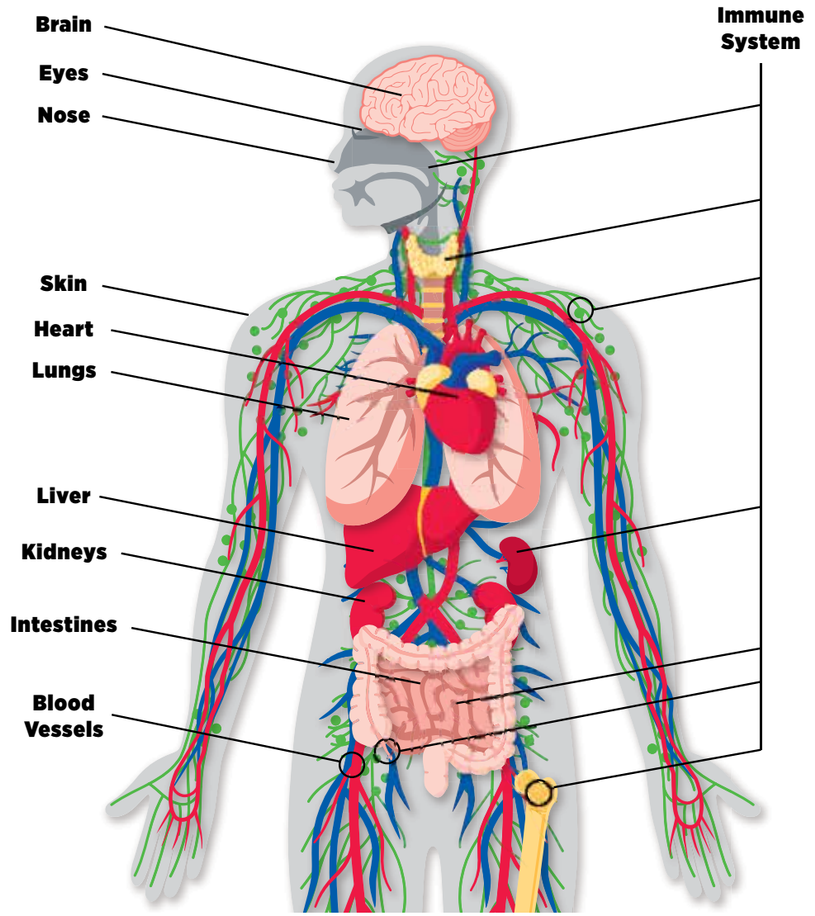
One possible explanation for the widespread damage seen in some patients who have COVID-19 is an overactive inflammatory response (69)(67). This can lead to a condition known as cytokine-release syndrome and severe, systemic inflammation. Inflammation in the lungs can progress to acute respiratory distress syndrome (ARDS), causing difficulty breathing and low blood oxygen levels. If unchecked, ARDS can progress to respiratory failure, which is the cause of death in many fatal COVID-19 cases. In addition, uncontrolled cytokine-release syndrome can lead to failure of other organs, most notably the heart, liver, and kidneys. Another explanation for the widespread damage in some patients who have COVID-19 is that cells lining the blood vessels can become damaged by the virus and/or the inflammatory response, which triggers abnormal blood clotting (67). This, in turn, can cause widespread organ damage.

Not everyone who becomes infected with SARS-CoV-2 goes on to develop symptoms of COVID-19; these people are said to be asymptomatic. Even among people who develop symptoms, there is a wide diversity in the severity of the disease. Gaining a deeper understanding of how infection with SARS-CoV-2 causes severe disease and what determines how severe disease will be for an individual are areas of intensive research investigation.

STATE OF THE COVID-19 EPIDEMIC

As of July 31, 2020, 17,622,478 people worldwide have been diagnosed with COVID-19, and more than 680,165 people have died from the disease (61). At that time, the United States accounted for more than one in every four recorded cases of COVID-19 and almost one in every four recorded deaths from the disease. As with the burden of cancer, certain segments of the U.S. population have shouldered a disproportionate

FIGURE 5 BEYOND THE LUNGS: COVID-19 AFFECTS MANY PARTS OF THE BODY



Coronavirus Disease 2019 (COVID-19) is best known as a disease of the lungs. In severe cases it can cause pneumonia and acute respiratory distress syndrome (ARDS), which is associated with difficulty breathing and low blood oxygen levels. If unchecked, ARDS can progress to respiratory failure, which is the cause of death in many fatal COVID-19 cases. As physicians and researchers learn more about COVID-19, an increasing number of organs and organ systems beyond the lungs are being found to be affected by the disease. Among the parts of the body most frequently affected by COVID-19 are the heart, brain, kidneys, intestines, blood vessels, blood, and immune system. Understanding the effects on blood vessels, blood, and immune system is a particularly active area of research investigation because an overactive inflammatory response and abnormal blood clotting are emerging as important factors in severe disease. Effects of COVID-19 on the skin, liver, eyes, and nose have also been reported in some patients.

Data from (67)(68)

burden of COVID-19 (see sidebar on **Disparities in the Burden of COVID-19 in the United States,** p. 30).

COVID-19 has spread swiftly around the world. The virus that causes the disease is predominantly spread through close contact from person to person when an infected person coughs, sneezes, or talks, releasing droplets that contain the virus into the air (75). These droplets can land in the mouths or noses of people who are nearby or possibly be inhaled into the lungs. Researchers continue to learn more about the ways in which the virus can be spread, with some data suggesting that in a few cases it might be possible that a person can become infected after touching a surface or object that has the virus on it and then touching his or her own mouth, nose, or possibly eyes (75). Infected individuals can spread the virus even before they develop symptoms of the disease or even if they never develop symptoms (76)(77). Given current knowledge of how SARS-CoV-2 is spread, the CDC recommends the following prevention strategies: washing hands frequently; avoiding close contact with people who don't live in your household by staying six feet apart; covering your mouth and nose with a cloth face cover when around other people; covering your mouth and nose when you cough and sneeze; cleaning and disinfecting frequently touched surfaces daily; and monitoring your health daily (78). In the absence of a SARS-CoV-2 vaccine, these prevention strategies are critical to limiting infection with the virus and, therefore, the morbidity and mortality of COVID-19, with one study estimating that mandates requiring the use of face masks in public had prevented from 230,000 to 450,000 cases of COVID-19 by May 22, 2020 (79).

The presentation of disease experienced by individuals who are infected with SARS-CoV-2 covers a wide spectrum, from no symptoms, to mild disease, to severe disease, to critical disease and even death. Advanced age (age 65 and older), sex (male), and having certain chronic health conditions, such as chronic kidney disease, chronic obstructive pulmonary disease (COPD), obesity, heart failure, coronary artery disease, sickle cell disease, diabetes, and a weakened immune system, increase a person's risk of severe COVID-19. Other health conditions, including asthma and high blood pressure, have also been linked to an increased risk of severe COVID-19, but additional research is needed to confirm these associations. One recent study showed that patients with COVID-19 who had underlying chronic health conditions were six times more likely to be hospitalized and 12 times more likely to die compared with those who had no underlying chronic health conditions (73). However, healthy patients of any age and sex can develop severe disease (80).

Based on current research, it seems that patients with cancer who develop COVID-19 might be at increased risk for severe disease and for death from the disease (81)(82)(83)(84). Patients who have a blood cancer appear to be at

DISPARITIES IN THE BURDEN OF COVID-19 IN THE UNITED STATES

Not all segments of the U.S. population have shouldered the burden of Coronavirus Disease 2019 (COVID-19) equally. Examples of such disparities include:

Hispanics

Hispanics account for about **18 percent of the U.S. population,** but **34 percent of COVID-19 cases** (70) (71).

African Americans

African Americans account for about **13 percent of the U.S. population,** but **20 percent of COVID-19 cases** and **23 percent of deaths** from the disease (70) (71).

American Indians/Alaska Natives

American Indians/Alaska Natives have a **rate of hospitalization for COVID-19 that is five times higher** than the rate of hospitalization for COVID-19 among whites (72).

Men

Men account for about **49 percent of cases of COVID-19 in the United States,** but **55 percent of deaths** from the disease (73).

Age 75+

People age 75 and older account for **10 percent of COVID-19 cases,** but **58 percent of deaths** from the disease (70).

Children from Racial and Ethnic Minorities

Hispanic and African American children have SARS-CoV-2 infection rates that are more than **seven times** and **five times higher**, respectively, than white children (74).

Adapted from (14)

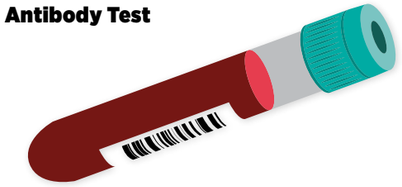
HOW CAN WE TEST FOR SARS-COV-2?

There are two types of SARS-CoV-2 tests: viral tests and antibody tests.

Viral Test

- Determines if a patient is currently infected with SARS-CoV-2; cannot determine if a person was previously infected.
- The samples tested are nasal or throat swabs, or saliva samples.
- The sample is tested either using a technique called PCR to determine whether the virus's genetic material is present or using other techniques that determine whether specific virus proteins, or antigens, are present.
- Antigen tests produce results more quickly than PCR tests, but they may be less sensitive meaning they may be less able to correctly identify those who are infected and, therefore, may miss some people who are infected.

Antibody Test



- Determines if a patient was previously infected with SARS-CoV-2; cannot determine if a person is actively infected.
- The samples tested are blood samples.
- The sample is tested to determine whether proteins called antibodies that the patient's immune system would have made during a previous infection with SARS-CoV-2 are present.

greatest risk. Research is underway to understand whether differences in COVID-19–related deaths among patients with cancer are a result of the cancer, the cancer treatment, or other factors. It is also important that patients with cancer are adequately represented in clinical trials assessing the safety and effectiveness of vaccines and treatment for COVID-19. Without such research, we cannot ensure that these agents will benefit patients with cancer.

DETECTING SARS-COV-2 AND COVID-19

Timely testing to identify those who are or have been infected with SARS-CoV-2 is a crucial step in understanding and controlling the COVID-19 pandemic (see sidebar on **How Can We Test for SARS-CoV-2?** p. 31). Without knowledge of who is infected, it is challenging to implement appropriate measures to prevent further spread of the virus and to understand when such measures can be eased.

New technologies in the form of symptom and contact tracing apps for smartphones are being used to track new COVID-19 cases and identify "hot spots" of infection in real time (85). Having this information has the potential to allow local hospitals and health care systems to better prepare for surges in new cases; however, it remains to be determined whether these apps will be effective at controlling disease spread. Large sets of data collected through these apps can also be used by researchers to deepen scientific understanding of SARS-CoV-2 and the symptoms related to COVID-19, as well as to identify potential risk factors and disparities related to infection with the virus and disease severity (86)(87).

CLINICAL MANAGEMENT OF COVID-19

Infection with SARS-CoV-2 causes a wide range of symptoms and disease severity (see **Understanding the Biology of SARS-CoV-2 Infection and COVID-19,** p. 27). More than 80 percent of people who are diagnosed with COVID-19 have mild symptoms and do not require hospitalization (73)(81). Among those patients who require hospitalization, about 16 percent have critical disease and require admission to the intensive care unit (73). In some cities, the number of patients requiring hospitalization has overwhelmed the capacity of hospitals to care for them.

As of July 31, 2020, no therapeutics have been approved by the FDA to treat patients who have COVID-19. Until such therapeutics are available, the clinical management of COVID-19 centers around treating symptoms (80). For example, patients with low blood oxygen levels are first placed on their stomach in the prone position. If this does not improve blood oxygen levels, patients are given supplemental oxygen or receive invasive mechanical ventilation. Those patients who experience kidney failure receive dialysis and those who have abnormal blood clotting are treated with anticoagulants such as heparin (88).

Although no therapeutics have been approved by the FDA for treating patients who have COVID-19, the agency authorized the emergency use of an investigational antiviral therapeutic called remdesivir for treating patients who have severe COVID-19 in May 2020 (89). Remdesivir was already under development as a potential treatment for infection with several viruses, including Ebola virus. The emergency use was granted based on results from a clinical trial that showed that treatment with remdesivir reduced the median recovery time for patients who had severe COVID-19 from 15 days to 11 days (90). Unfortunately, there is a limited supply of remdesivir. Therefore, the NIH recommends that remdesivir be prioritized for use in hospitalized patients with COVID-19 who require supplemental oxygen but who are not on high-flow oxygen, noninvasive ventilation, mechanical ventilation, or extracorporeal membrane oxygenation (91).

The NIH also recommends the use of dexamethasone, which is a steroid that is frequently used to dampen inflammation, as a treatment for patients with COVID-19 who are mechanically ventilated and patients with COVID-19 who require supplemental oxygen but who are not mechanically ventilated (91). This recommendation is based on results from a large clinical trial that showed that a 10-day course of dexamethasone reduced the risk of death by about a third (36 percent) among hospitalized patients with COVID-19 who were mechanically ventilated and by about a fifth (18 percent) among hospitalized patients with COVID-19 who required supplemental oxygen but who were not mechanically ventilated (92).

There are many other therapeutics being investigated as potential treatments for COVID-19 because the global research community has responded robustly to this pandemic. These investigational therapeutics work in a wide variety of ways to combat COVID-19 (see sidebar on **What Types of Treatment Are Being Investigated for COVID-19?** p. 33). As of July 31, 2020, the FDA reported that there were more than 570 drug development programs in planning stages and that the agency had reviewed more than 270 trials of potential treatments for COVID-19 (93). One area of active research investigation is the repurposing of therapeutics that are already under investigation or have been approved by the FDA for other uses because we already have information about dosage, toxicity, and adverse effects for these therapeutics, which can accelerate the pace of therapeutic development and approval relative to the development of novel therapeutics.

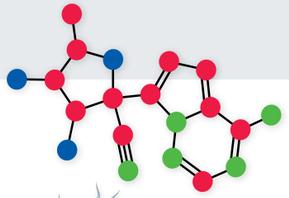
In addition to developing therapeutics for treating patients with COVID-19, stakeholders in the global research community are working collaboratively to develop SARS-CoV-2 vaccines. In the United States, on April 17, 2020, the NIH announced a public-private partnership—Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV)—to develop a coordinated research strategy for prioritizing and accelerating the development of the most promising vaccines and therapeutics against COVID-19. ACTIV brings together the NIH and other U.S. government agencies; the European Medicines Agency (EMA); and representatives from academia, philanthropic organizations, and numerous biopharmaceutical companies. Also in the United States, the National Institute of Allergy & Infectious Diseases (NIAID) has founded a new clinical trial network, the COVID-19 Prevention Trials Network (COVPN), to address the challenges of patient enrollment in clinical trials and the need to recruit volunteers from parts of the country that are experiencing a severity of the COVID-19 epidemic. COVPN comprises the HIV Vaccine Trials Network, the HIV Prevention Trials Network, the Infectious Diseases Clinical Research Consortium, and the AIDS Clinical Trials Group and will leverage existing infrastructure to engage communities to facilitate the enrollment of the thousands of volunteers needed for late-stage clinical trials of promising vaccines against SARS-CoV-2.

CANCER IN THE MIDST OF COVID-19

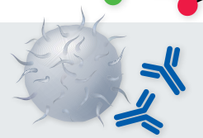
The COVID-19 pandemic has created many challenges across the continuum of cancer care, with individual health care systems and institutions adjusting cancer screening, diagnosis, treatment, and follow-up care to respond to the rapidly evolving situation. Some cancer care has continued, some was altered, and some was suspended. Individuals who are scheduled for any form of cancer care should consult with their health care provider before their appointment.

WHAT TYPES OF TREATMENT ARE BEING INVESTIGATED FOR COVID-19?

A wide array of types of therapeutics are being investigated as potential treatments for COVID-19. These include:

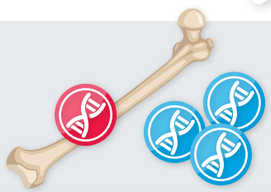


Antiviral Therapeutics
These therapeutics directly target SARS-CoV-2, preventing virus infection and spread.



Immunomodulators
These therapeutics are designed to dampen the patient's inflammatory response following infection with SARS-CoV-2.

Neutralizing Antibody Therapies
These treatments include manufactured antibodies, animal-sourced antibody therapies, and blood-derived products such as convalescent plasma and hyperimmune globulin, which contain antibodies taken from people who have previously had COVID-19. The aim of these treatments is to reduce the level of virus shortly after infection and thereby protect against severe disease. Such antibodies could also be used to prevent SARS-CoV-2 infection in those known to be at high risk.

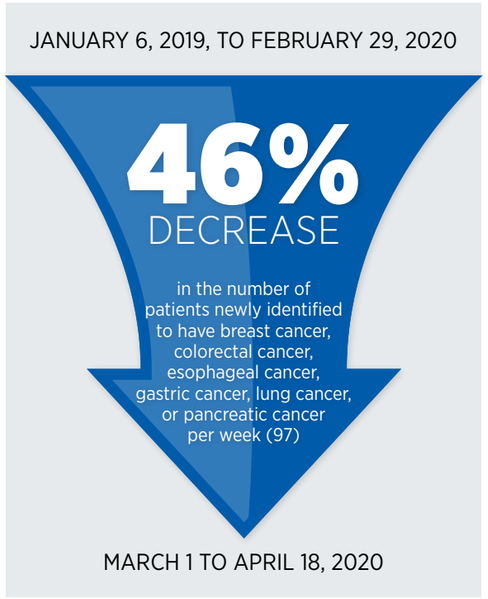


Cell Therapies
These treatments include cellular immunotherapies and other types of cells, such as stem cells, and related products. They work to combat COVID-19 in a variety of ways.

Gene Therapies
These treatments are designed to modify or manipulate the expression of a gene or to alter the biological properties of living cells for therapeutic use.

There is deep concern about the consequences that delays in cancer screening, diagnosis, and treatment will have on outcomes for patients with cancer (10)(94). Data from electronic medical records from 190 hospitals spanning 23 states show that the number of screening tests for early detection of cervical, breast, and colon cancer conducted in the United States plummeted by 85 percent or more after the first COVID-19 case was reported in the United States on January 20, 2020 (95), and a recent survey of patients with cancer found that 79 percent of those who are actively undergoing treatment had to delay some aspect of their care as a result of COVID-19, including 17 percent who reported delays to their cancer treatment (96). It will take years to determine the consequences of all the delays, but researchers at the NCI have estimated that there will be at least 10,000 additional deaths from breast cancer and colorectal cancer over the next decade in the United States as a result of the negative impact that the COVID-19 pandemic has had on screening and treatment for these two types of cancer (10).

Several decisions made by the FDA since the onset of the pandemic have provided certain patients with cancer alternative treatment options that have the potential to reduce the need for frequent visits to health care facilities, which is an important consideration for patients during the COVID-19



pandemic. 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. 97). Pembrolizumab is administered intravenously, meaning 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 that can reduce the number of times a patient must visit a health care facility for treatment. In July 2020, the FDA approved a tablet form of the epigenetic therapeutic decitabine for treating certain patients with myelodysplastic syndrome (MDS) (see **Using Epigenetic Therapy to Treat Cancer,** p. 90). Given that decitabine is normally given intravenously, the new tablet provides patients with an option that can reduce the number of health care–facility visits. In July 2020, the FDA also approved a version of the commonly used combination of HER2-targeted therapeutics trastuzumab (Herceptin) and pertuzumab (Perjeta) that can be given subcutaneously (under the skin), rather than given intravenously as normal. Although this still needs to be administered by a health care provider, it can be given at a patient's home.

CANCER RESEARCHERS WORKING TO COMBAT THE COVID-19 PANDEMIC

Cancer researchers are uniquely positioned to respond to many of the challenges posed by COVID-19, and many have refocused their expertise to combat the unprecedented global pandemic. For example, the NCI is lending its expertise and cutting-edge resources to conduct research that will contribute to the global effort to address COVID-19 (98). The NCI has a world-class serology facility that works to standardize human papillomavirus (HPV) antibody testing, the HPV Serology Laboratory. This laboratory is now being used to advance COVID-19 serological testing and is part of a broader effort within the NIH to increase our understanding of SARS-CoV-2 infection and the immune response to the SARS-CoV-2 virus. Other researchers at the NCI are part of an initiative that includes several NIH institutes to better understand the impact of a person's genome on COVID-19 outcomes and to screen compounds for use as potential COVID-19 treatments. Yet others at the NCI are building a large longitudinal cohort of people with cancer and COVID-19, the NCI COVID-19 in Cancer Patients Study (NCCAPS), to gain information that will support better treatment management for people with cancer and COVID-19 (99).

In addition, cancer researchers around the world are working together to leverage their experience to accelerate SARS-CoV-2 vaccine and therapeutic development, and to repurpose treatments used in cancer care for the benefit of patients with COVID-19. An area in which cancer researchers have vast expertise is the collection and sharing of "big data." This expertise is being harnessed to better understand the effect of COVID-19 on patients with cancer. The goal is to obtain clinical and other patient-related information on a large enough scale to answer questions about the epidemiology of COVID-19 among patients with cancer as well as clinical data on the effectiveness of COVID-19 diagnostics, vaccines, and treatments in these patients. Several cancer organizations as well as multi-institutional teams have already launched initiatives to catalyze data sharing (see **Table 3,** p. 35).

ADAPTING CANCER RESEARCH AND MEDICINE IN THE COVID-19 ERA

As highlighted throughout this report and in previous AACR Cancer Progress Reports, the past decade has been an incredible time in cancer research, leading to unprecedented progress against cancer. However, the COVID-19 pandemic forced cancer research laboratories to shutter or to refocus to work on COVID-19-related projects instead of cancer. Attention diverted away from cancer research due to the pandemic, although necessary, will come at a real cost to progress against cancer in the future.

One area of research that has been significantly disrupted during the COVID-19 pandemic is the conduct of all types of clinical trials, including cancer clinical trials. One report estimated that globally, there was a 74 percent decrease in the number of new patients enrolling in clinical trials during the

TABLE 3 SELECTED REGISTRIES COLLECTING DATA ON PATIENTS WITH COVID-19 AND CANCER

Project	Goal
COVID-19 and Cancer Consortium (CCC19)	Collect and quickly share information on patients with cancer and COVID-19 on a large scale.
UK Coronavirus Cancer Monitoring Project	Pinpoint and collect data from every case of COVID-19 in patients with cancer in the United Kingdom.
Thoracic cancERs international coVid 19 cOLlaboraTion (TERAVOLT)	Collate international data on patients with thoracic cancers who have COVID-19.
ASH Research Collaborative COVID-19 Registry for Hematologic Malignancy	Gather data on patients with COVID-19 who have or have had a hematologic condition.
ASCO Survey on COVID-19 in Oncology (ASCO) Registry	Aid in the identification of the impact of COVID-19 on cancer care and in patients with cancer.
ESMO-CoCARE Registry	To quickly gather data from health care professionals on SARS-CoV-2 impact in patients with cancer.
COPE Consortium	To identify risk factors for COVID-19 infection and to produce data on clinical outcomes over the near and long term with a focus on the impact of the COVID-19 epidemic on health care workers and persons living with cancer
St. Jude's COVID-19 and Childhood Cancer Registry	Learn about the impact of SARS-CoV-2 in pediatric patient population and be better prepared to meet future challenges similar to COVID-19

*This list is not intended to be comprehensive

https://www.nature.com/articles/s43018-020-0065-z
https://ccc19.org/other-efforts

first two weeks of May 2020 compared with the same period in 2019 (100). More recent analysis from the same group indicates that enrollment in clinical trials has increased since the first two weeks of May 2020, but it remains 30 percent lower than before the COVID-19 pandemic (101). In the United States, it was estimated that the number of patients enrolled each week in NCI-sponsored clinical trials more than halved between early March and early April 2020 (102). A separate report found that only 20 percent of the U.S. institutions that were surveyed for the report were continuing to enroll patients in cancer clinical trials at pre-COVID-19 rates (103). Among the challenges to clinical trial enrollment and conduct are a decrease in the ability or willingness of patients to go to health care facilities and the limited availability of services such as radiology, surgery, and cardiology (104). All stakeholders are working together to adapt clinical trial practices to ensure that ongoing and new clinical trials can safely continue (104–106). Many of the adjustments to cancer clinical trial practice already made and being considered in response to the COVID-19 pandemic have the potential to lead to long-term positive changes (see sidebar on **Improving Cancer Clinical Trials during COVID-19 and Beyond,** p. 36).

There are many other challenges in cancer research posed as a result of the COVID-19 pandemic. One of the most concerning is that cancer research laboratories that were shuttered or were refocused to work on COVID-19-related projects instead of cancer will require significant time and resources to reopen and reestablish. It will be critical to provide support to the cancer research that has been interrupted, particularly that conducted by early-career, minority, and female investigators for whom losses to productivity due to the pandemic could have the potential to be career ending (107–109).

In addition, the COVID-19 pandemic has had an adverse impact across the continuum of cancer care (see **Cancer in the Midst of COVID-19,** p. 32). Addressing the delays in cancer screening, diagnosis, and treatment that have occurred since the beginning of the COVID-19 pandemic will require considerable time and innovative solutions. One approach being recommended by some professional

IMPROVING CANCER CLINICAL TRIALS DURING COVID-19 AND BEYOND

Clinical trials are critical for progress against cancer. Although the ongoing COVID-19 pandemic has disrupted many aspects of cancer clinical trials, all stakeholders have come together and responded in unprecedented ways to continue clinical research. Remarkable changes to the conduct of clinical trials have been proposed and/or implemented, many of which may be continued beyond the pandemic. The suggested changes are designed to ensure a patient-centric approach and to enhance patient safety and experience while improving clinical trial efficiency and outcomes. Some of the changes have the potential to improve long-standing challenges in clinical trials such as low enrollment of patients and a lack of diversity among those who do participate. Below are some examples of such recommendations across the various stages of the clinical trial process (105) (106):

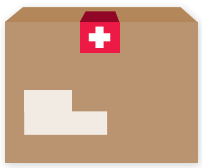
Clinical trial design and regulation:

- Prioritize and streamline the primary endpoints of the trial
- Enable remote trial monitoring
- Enable flexible electronic and remote consent

Patient enrollment (trial eligibility and screening):

- Reduce nonessential screening assessments
- Limit "in-person" screening assessments to a single visit
- Permit virtual visits and decentralized assessments

Delivery of care:



- Permit and train for low-risk therapeutic administration at home
- Implement easier routes of delivery of therapeutics, e.g., oral instead of intravenous
- Ship therapeutics to patient's home to minimize time in study center
- Use telemedicine when appropriate

Assessment of safety and efficacy:

- Reassess the need for and frequency of safety and efficacy assessments
- Direct patient reporting of symptoms/adverse effects
- Allow for diagnostic testing such as bloodwork/imaging to be performed locally to patients and when possible incorporated as part of regular clinical care
- Increase use of telemedicine
- Implement alternative safety assessment methods (for example, wearable technologies)
- Permit decentralized efficacy assessments in non–study centers and review centrally
- Consider surrogate efficacy markers (e.g., ctDNA and tumor markers)

organizations to overcome barriers to colorectal cancer screening during the ongoing COVID-19 pandemic is to increase the use of noninvasive stool-based tests because these can be undertaken at home, rather than requiring travel to a health care facility as is needed for a colonoscopy. Another approach being used to help ensure continuity of care for patients with cancer is the use of telemedicine in place of in-person visits. It is imperative that racial and ethnic minorities and other the underserved populations have access to the solutions to the cancer care challenges posed by the COVID-19 pandemic so as not to exacerbate existing cancer health disparities.

PREVENTING CANCER: IDENTIFYING RISK FACTORS

IN THIS SECTION YOU WILL LEARN:

- In the United States, four out of 10 cancer cases and almost half of all cancer-related deaths are associated with preventable risk factors.
- Tobacco use is the leading preventable cause of cancer.
- Nearly 20 percent of U.S. cancer diagnoses are related to excess body weight, alcohol, 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 could be prevented by HPV vaccination, but 46 percent of U.S. adolescents have not received the recommended doses of the vaccine.

Thanks to decades of research, we have identified several factors that increase a person's risk of developing and/or dying from cancer. Given that several of these risk factors such as smoking, excess body weight, unhealthy diet, exposure to ultraviolet (UV) radiation, and infection with certain pathogens can be avoided, many cases of cancer could potentially be prevented (see **Figure 6,** p. 38). Researchers estimate that more than 40 percent of the cancer cases diagnosed in the United States in 2014 and nearly half of all deaths from cancer were caused by one or more of these potentially avoidable cancer risk factors (110).

Many cancer risk factors are also associated with other chronic diseases, such as cardiovascular disease, respiratory diseases, and diabetes. Thus, public education and policy initiatives to reduce or eliminate exposure to potentially modifiable cancer risk factors have the potential to reduce the burden of several other diseases in addition to cancer. In fact, according to a recent report, middle-aged individuals (50 years old) who adhere to a low-risk, healthy lifestyle by never smoking, eating healthily, staying active, maintaining a healthy weight, and limiting alcohol consumption have a more than five years higher life expectancy free of major chronic diseases such as diabetes, cardiovascular diseases, and cancer compared with those who do not adopt such low-risk behaviors (111).

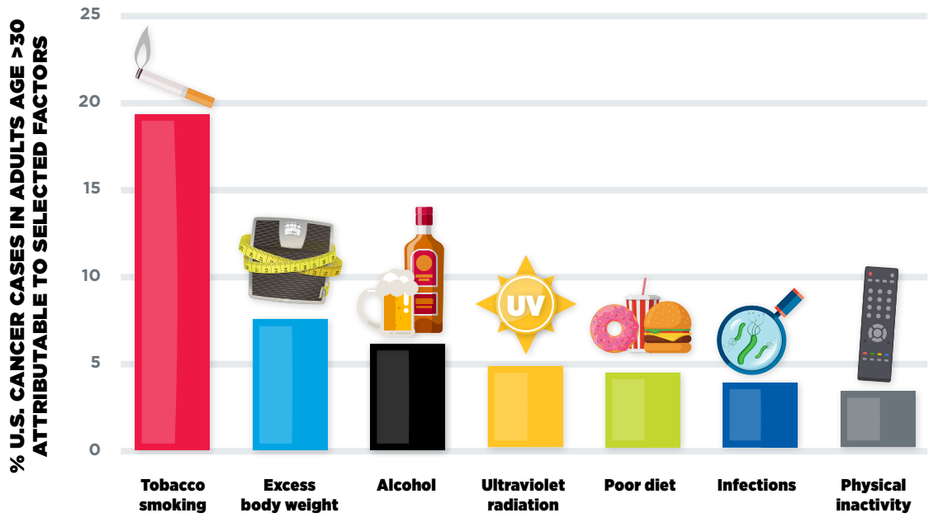
Unfortunately, federal support of cancer prevention research evaluating the leading risk factors of U.S. mortality and morbidity is seriously inadequate relative to the negative impact of these factors in the United States (112). Therefore, it is imperative that support for prevention research testing randomized interventions, especially those addressing multiple risk factors or causes, should become a national priority.

Another critical issue hindering improvement in public health is our inability to effectively communicate the current knowledge on avoidable cancer risk factors to the general population. According to some recent surveys, many individuals both in the United States and across the globe are still unaware of the significant cancer risks associated with obesity, physical inactivity, and alcohol use (113)(114). This emphasizes the continued need for widespread dissemination of our current knowledge of cancer risk factors, as well as the implementation of known preventive strategies to reduce risky behaviors. Targeted efforts are also needed for certain segments of the U.S. population, such as racial and ethnic minorities, and other underserved groups who are disproportionately exposed to many of the potentially avoidable risk factors and have not benefited equally from the existing cancer prevention and control interventions (115) (see sidebar on **Disparities in the Burden of Avoidable Cancer Risk Factors,** p. 39). Future interventions that are evidence-based, sustainable, targeted, and culturally tailored need to be implemented to benefit communities with the greatest need, thereby ensuring improved health outcomes for all Americans.

ELIMINATE TOBACCO USE

Tobacco use is the leading preventable cause of cancer because it exposes individuals to many harmful chemicals that damage DNA, causing genetic and epigenetic alterations that lead to cancer development (122)(123)(124). Smoking tobacco has been shown to increase the risk of developing 17 different types of cancer in addition to lung cancer (see **Figure 7,** p. 40). Fortunately, quitting at any age can reduce these risks. Researchers have found that quitting smoking allows new, healthy cells to actively replenish the damaged cells in the

FIGURE 6 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 cancer. Developing and implementing additional public education and policy initiatives could help further reduce the burden of cancers related to preventable cancer risk factors.

Data from (46). Figure adapted from (15)

lining of our airways leading to a protective effect against lung cancer (125). According to a recent report from the U.S. Surgeon General, smoking cessation reduces risk for many adverse health effects in addition to reducing risks from cancer, including cardiovascular diseases and chronic obstructive pulmonary disease (COPD) among others (126). In fact, quitting smoking can reduce the risk of premature death and add up to a decade to life expectancy. In addition to its health benefits, smoking cessation can also reduce the substantial financial burden on smokers and the health care system.

Thanks to the implementation of nationwide comprehensive tobacco control initiatives, cigarette smoking among U.S. adults has been declining steadily. In 2018, which is the most recent year for which data are available, 13.7 percent of U.S. adults age 18 and older smoked cigarettes, which is the lowest prevalence recorded since 1965 (116). Exposure to secondhand smoke, which increases the risk of lung cancer among nonsmokers, has also dropped substantially over the past three decades (127). Notably, 95 percent of adults

THE REAL COST

The FDA's national tobacco public education campaign, "The Real Cost", has prevented up to 587,000 U.S. youth and young adults from initiating smoking between February 2014 and November 2016 (131).

Half of these individuals might have gone on to become established adult smokers.

By preventing them from becoming established smokers, "The Real Cost" will save an estimated >$53 billion by reducing smoking-related costs such as early loss of life, medical care, lost wages, lower productivity, and increased disability.

DISPARITIES IN THE BURDEN OF AVOIDABLE CANCER RISK FACTORS

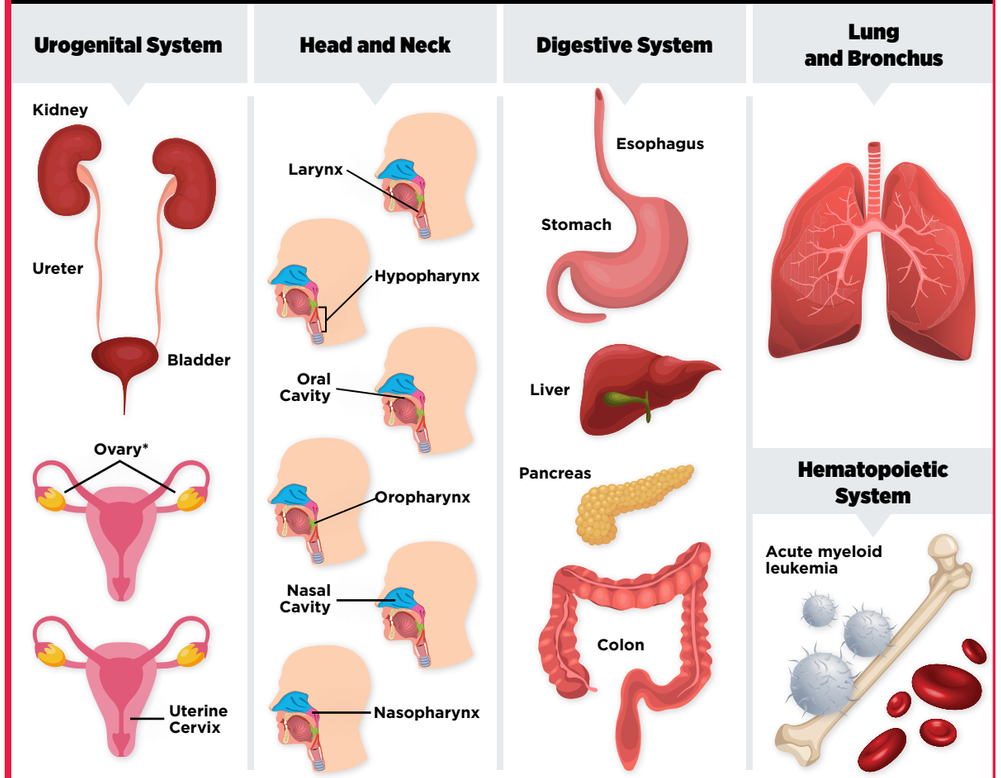
There are considerable disparities in the exposure to avoidable cancer risk factors among certain segments of the U.S. population, such as:

5 TIMES LESS LIKELY	Individuals with a graduate degree are more than **5 times less likely** to smoke cigarettes than those with a high school education or less (116).
1.5 TIMES LESS LIKELY	Heterosexual individuals are **1.5 times less likely** to smoke cigarettes compared to LGBT individuals (116).
57% vs **40%**	Prevalence of obesity is higher among Black women (57%) compared with white women (40%) (117).
31% vs **23%**	Hispanics (31.7%) have the highest prevalence of physical inactivity, followed by non-Hispanic Blacks (30.3%) and non-Hispanic whites (23.4%) (118).
HIGHEST DEATH RATES	Non-Hispanic American Indian/Alaska Natives have the highest alcohol-related death rates among all racial and ethnic groups (119).
SUNSCREEN USE	Only 6% of non-Hispanic Black and 24% of Hispanic fifth-graders reported using sunscreens compared with 45% of non-Hispanic whites (120).
57% vs **47%**	Adolescents living in metropolitan areas are more likely to be up to date with HPV vaccination (57%) compared with those in nonmetropolitan areas (47%) (121).

who smoke report trying their first cigarette before the age of 21. Therefore, preventing or delaying the initiation of tobacco product use among youth and young adults may have a significant positive impact on smoking-related health outcomes (128). Hence, it is also encouraging that initiation of tobacco products, including cigarettes, has been declining among youth and young adults with a significantly lower percentage of individuals ages 12 to 24 reporting smoking initiation in 2018 compared with 2008 (129). To further accelerate this progress against tobacco use among youth and young adults a new policy was implemented on December 20, 2019, when the U.S. Congress signed legislation amending the Federal Food, Drug, and Cosmetic Act, and raising the federal minimum age of sale of all tobacco products from 18 to 21 years (130).

Despite these positive trends we cannot overlook the fact that in the United States more than 49 million adults and nearly

FIGURE 7 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.

* Certain subtypes of ovarian cancer

Figure adapted from (1)

11 million youth and young adults reported using a tobacco product in 2018 and 2019, respectively (116)(132). In addition, according to recent estimates around 58 million nonsmokers, including 14 million children ages 3 to 11 years, were exposed to secondhand smoke between 2013 and 2014 (127). There are striking sociodemographic disparities in the use of tobacco products as well as secondhand smoke exposure. For instance, tobacco use is higher among non-Hispanic American Indian/Alaska Native adults compared with other racial or ethnic groups, among residents of the Midwest or southern United States compared with the rest of the country, among individuals with lower levels of household income, among adults who were uninsured, and among individuals with disabilities or serious psychological distress (116).

It is imperative that all stakeholders continue to work together to identify evidence-based, population-level interventions such as tobacco price increases, public health campaigns, age and marketing restrictions, cessation counseling and medications, and smoke-free laws to reduce

MORE THAN **40%** of smokers never receive advice regarding smoking cessation from their health care providers (126).

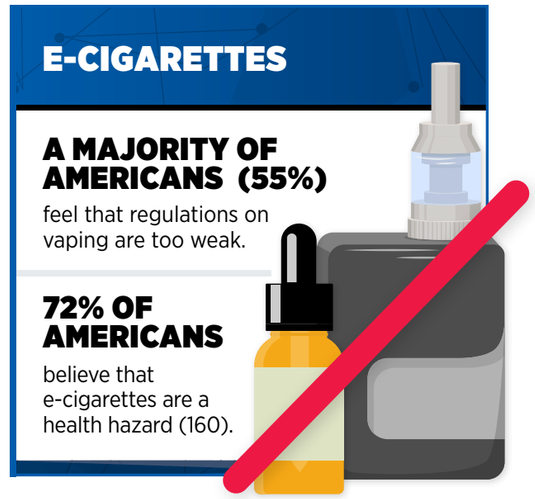
smoking rates and smoking-related cancer burden in the United States. Two recent reports indicate that innovative interventions offered in unique clinical settings, such as the Emergency Department while patients present with semi-urgent or nonurgent treatments, or at pediatricians' offices while parents are visiting with their child's doctor, can be effective in increasing smoking cessation among adults (133) (134). These findings are important since each year over half of adult smokers try to quit smoking but less than 10 percent are successful (126). Notably, FDA-approved therapeutics and behavioral counseling have both been shown to improve the chances of quitting and using them together can double the odds of quitting successfully (126).

The use of other combustible tobacco products (for example, cigars), smokeless tobacco products (for example, chewing tobacco and snuff), and waterpipes (hookahs) is also associated with adverse health outcomes including cancer (135). Electronic cigarettes (e-cigarettes) are a rapidly emerging tobacco product. An alarming trend in recent years is the growing popularity of e-cigarettes among U.S. youth and young adults. E-cigarettes were first introduced to the U.S. market in 2007, and since 2014 they have been the most commonly used tobacco product among U.S. middle and high school students (136) (see sidebar on **E-Cigarettes: What Have We Learned and What Do We Need to Know?** p. 42).

E-cigarettes come in flavors that appeal to youth and young adults and deliver very high levels of nicotine, an extremely addictive substance that is harmful to the developing brain (153). The continued surge in e-cigarette use among this vulnerable population has been an ongoing public health challenge. Not only is the percentage of current users increasing every year, but recent data also indicate that more e-cigarette users are starting to use these products at a younger age (154) (140) (155). The percentage of youth who had used their first e-cigarette by age 14 increased from 8.8% in 2014 to 28.6% in 2018 (156). Exposure to secondhand aerosol (SHA) from e-cigarettes can expose nonusers to potentially harmful substances including nicotine, carbonyl compounds, tobacco-specific nitrosamines, heavy metals, and glycols. Concurrent with the recent surge in e-cigarette use among U.S. youth and young adults, there has also been an increase in SHA exposure among U.S. middle and high school students (157). This is especially concerning since individuals who are exposed to SHA are more susceptible to using e-cigarettes or cigarettes later in life (157).

The availability of kid-friendly flavors, exposure to product marketing, and misperceptions about harm are some of the reasons behind the continued use of e-cigarettes among youth and young adults. In fact, according to a 2019 national survey, 20 percent of young adults in the U.S. perceived e-cigarettes as "harmless" (158). While a more recent survey from the U.K. suggests an increase in the proportion of adults age 16 and older who perceive e-cigarettes as harmful, post– E-cigarette, or vaping, product use-associated lung injury (EVALI) outbreak, whether the same holds true in the United States and whether such change in perception leads to a reduction in future e-cigarette use among youth and young adults remains to be evaluated (159).

For the most part, efforts to limit the rapid spread of e-cigarette use among youth and young adults have been inadequate. 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 the 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 **Supporting Public Health Policies to Reduce the Use of Tobacco Products,** p. 137). It is imperative that all stakeholders continue to work together to determine the long-term health outcomes associated with e-cigarettes and identify new and effective strategies to implement population-level regulations to reduce e-cigarette use among youth and young adults.



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 (137). By December 2017, Juul held the largest market share of any e-cigarette in the U.S. (138).

Constituents and user's exposure to toxicants

- One Juul pod delivers as much nicotine as a pack of cigarettes; exposure to other toxic substances is lower.
- 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 (137).

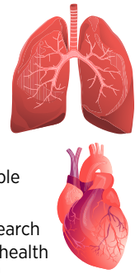
Use

- Use is highest among youth and young adults.
- Use among middle and high school students continues to rise sharply: middle-school [3.3% in 2017; 5% in 2018; 11% in 2019]; high school [12% in 2017; 21% in 2018; 28% in 2019] (132) (139). Juul is the most commonly used brand; most current users prefer flavored e-cigarettes such as fruit, menthol or mint, and candy/desserts/sweets (140).

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; the use of modifiable (mods) devices, which allow users to adjust the amount of nicotine delivered, is especially concerning. According to a recent report, young adults using modifiable (versus pen-like) e-cigarette devices smoked greater than six times as many cigarettes after transitioning (141).

Human health effects



- There are early indications that vaping can pose significant risks to vascular and respiratory health (142) (143).
- Preliminary studies indicate that people who vape may have similar carcinogens in their urine as do combustible cigarette users (144).
- 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.

Possible harm reduction compared to combustible tobacco

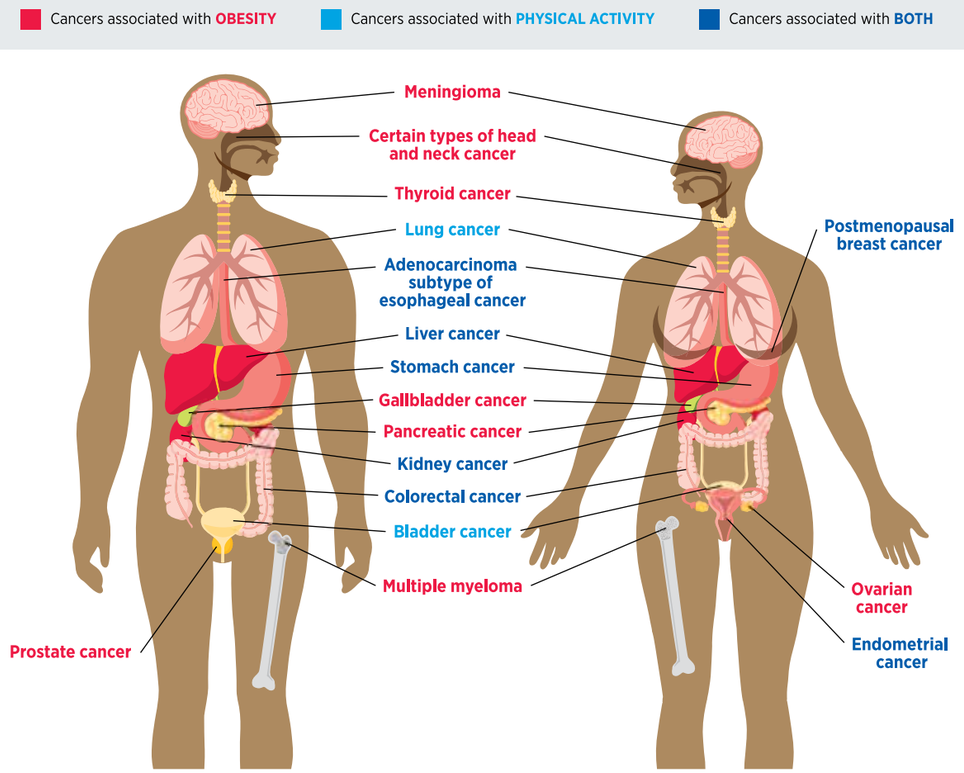
- Completely switching to e-cigarettes from regular use of conventional cigarettes can reduce exposure to toxic chemicals.

Poisoning, injuries, and other 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.
- The FDA is aware of and investigating the causes of 35 cases of seizures following e-cigarette use, mostly in youth and young adults, since 2010 (145).
- E-cigarette, or vaping, product use-associated lung injury (EVALI)—The CDC, FDA, and the state health authorities reported a sharp rise in symptoms or cases of EVALI since August 2019, a peak in September, and a gradual decline since then (146-148). By February 18, 2020, a total of 2,807 hospitalized cases or deaths were reported to CDC (149). Researchers identified that vitamin E acetate, an additive in some tetrahydrocannabinol (THC)-containing e-cigarettes, or vaping products, was strongly linked to the EVALI outbreak (150) (151). THC is the primary psychoactive ingredient in marijuana. Eighty-two percent of patients with EVALI reported using THC products and 78 percent, especially adolescent users, reported obtaining their products only from informal sources such as family, friends, and in-person or online dealers.

Adapted from (152)

FIGURE 8 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 activity are shown in light blue; cancers that are associated with both are shown in dark blue.

Data from (162–168). Figure adapted from (40).

MAINTAIN A HEALTHY WEIGHT, EAT A HEALTHY DIET, STAY ACTIVE, AND AVOID SEDENTARY BEHAVIOR

Nearly 20 percent of new cancer cases and 16 percent of cancer deaths in U.S. adults are attributable to a combination of being overweight or obese, poor diet, physical inactivity, and excessive alcohol consumption (110). Being overweight or obese as an adult increases a person's risk for 15 types of cancer whereas being physically active reduces risk for nine types of cancer (see **Figure 8,** p. 43). Therefore, maintaining a healthy weight, being physically active, avoiding sedentary behavior, and consuming a balanced diet are effective ways a person can lower the risk of developing or dying from cancer

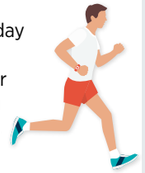
REDUCE YOUR RISK FOR CANCER BY MAINTAINING A HEALTHY WEIGHT, BEING PHYSICALLY ACTIVE, AND CONSUMING A BALANCED DIET

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 (178):

Maintain a healthy weight (body mass index [BMI] between 18.5 and 24.9) because 15 types of cancer have been causally linked to being obese or overweight (see **Figure 8, p. 43**).

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

Be physically active as part of everyday life; regular physical activity can decrease risk for nine types of cancer (see **Figure 8, p. 43, and sidebar on Physical Activity Guidelines, p. 47**).

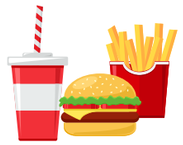


Limit intake of sugar-sweetened drinks because these lead to weight gain; drink mostly water.

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

If consumed at all, limit alcoholic drinks, because alcohol consumption can increase risk for six types of cancer (see **Figure 9, p. 48**).

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

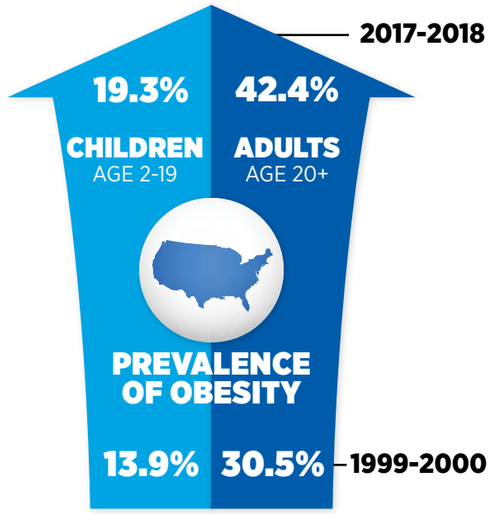


For mothers, breastfeed baby, if able.

Source: https://www.wcrf.org/dietandcancer/resources-and-toolkit and (178)

(see sidebar on **Reduce Your Risk for Cancer by Maintaining a Healthy Weight, Being Physically Active, and Consuming a Balanced Diet,** p. 44). Identifying the ways by which obesity, unhealthy diet, and physical inactivity increase cancer risk and quantifying the magnitude of such risks are areas of active research investigation (161).

In 2014, an estimated seven and eight percent of all U.S. cancer cases and deaths, respectively, were attributable to excess body weight. Beyond cancer, obesity increases the risk of developing several other health problems including type 2 diabetes, high blood pressure, heart disease, stroke, liver disease, and kidney disease (169). Therefore, it is concerning that in the U.S. and around the globe the prevalence of obesity has been rising steadily. In the United States, 42 percent of adults age 20 and older were obese in 2018, and according to a recent projection, by the year 2030, nearly 50 percent of all U.S. adults age 18 and older will have obesity (117)(170). An area of particular concern is childhood obesity, since for many children excess body weight extends into adulthood



and increases the risk of adverse health outcomes (171–173). In 2018, nearly 20 percent of children ages 2 to 19 years were obese (174). Concurrent with the steady rise in obesity rates in the United States, the incidence of several obesity-associated cancers has also been rising at an alarming rate, especially among young adults (175)(176). While further research is needed to elucidate whether weight loss can effectively mitigate cancer risks and curb these emerging trends, interventions that encourage people to maintain a healthy weight are certainly a top priority in public health.

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 food and beverages and insufficient physical activity play a significant role (169). In the United States, more than 5 percent of all newly diagnosed cancer cases among adults are attributable to eating a poor diet (179). Low intake of healthy foods such as whole grains, fruits, nuts, and seeds combined with high consumption of unhealthy foods such as sugar-sweetened drinks and high levels of red and processed meats are, in fact, responsible for one in five deaths globally (180).

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 U.S. Department of Health and Human Services and the U.S. Department of Agriculture in the 2015–2020 Dietary Guidelines for Americans (181). Unfortunately, the burden of many diet-related diseases, including cancer, is disparately high in low-income neighborhoods lacking access to healthy food retailers such as supermarkets, while having an overabundance of convenience stores with unhealthy and fast food options (169). One initiative that has been effective in increasing the consumption of healthy food and lowering the rates of obesity among children from low-income families is the Special Supplemental Nutrition Program for Women Infants and Children (WIC) (182). Data from more than 12 million children ages 2 to 4 whose families are enrolled in the WIC program show that obesity rates declined from 16 percent in 2010 to less than 14 percent in 2016. A potential factor that may have contributed is the consumption of more fruit, vegetables, and whole wheat products which are made available through this program (183). Initiatives such as WIC are extremely important given that obesity during early childhood is associated with sustained overweight or obesity in adolescence or adulthood and that obesity during adolescence can increase the risk of developing cancer later in life.

Evidence-based public policies can play an important role in promoting healthy dietary habits. In this regard, the FDA 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 (184). Another approach proposed in a recent report suggests that labeling food and beverages with information on how much exercise it would require to burn off its caloric content might be an effective way of encouraging people to make healthier food choices (185). Yet 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 (186). SSBs are a major contributor to caloric intake among U.S. youth and adults (187)(188). Thus, it is encouraging that since the implementation of taxes on SSBs, there are already some indications of reduction in consumption, in several cities within the U.S. and in some cases in lower-income, racially and ethnically diverse neighborhoods (189) (190)(191). Interestingly, according to some experts, taxing the amount of sugar in an SSB instead of the volume of the beverage could generate significantly greater health and economic benefits (192)(193). Continued research is necessary to identify the optimal approaches to regulating food and

SUSTAINED WEIGHT LOSS

Sustained weight loss, even modest amounts, is associated with lower breast cancer risk for women age ≥50 years (177).

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

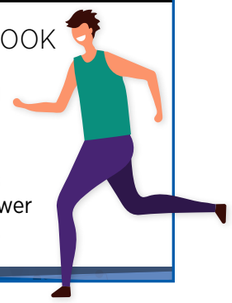
Three percent of overall cancer cases in the United States can be attributed to physical inactivity (110). According to a recent report, being sedentary (inactive) for 13 or more hours per day can increase the risk of dying from cancer by 82 percent (194). Engaging in recommended amounts of physical activity can lower the risks for developing nine types of cancer (see **Figure 8,** p. 43 and sidebar on **Physical Activity Guidelines,** p. 47), and in fact there is emerging evidence that there may be risk reduction for even more cancer types (165–167). Physical activity also reduces the risk of dying from cancer. For example, research shows that replacing just 30 minutes of sedentary behavior with a moderately intense physical activity such as biking can reduce the risk of dying from cancer by 30 percent (194); running, even once a week, can significantly reduce the risk of dying from cancer and cardiovascular diseases (195). Considering this evidence, it is concerning that more than 1 in 7 adults across all U.S. states and territories are physically inactive, and only a quarter of children and youth ages 6 to 17 get the recommended hour of moderate-to-vigorous exercise a day (118)(196). 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 all Americans.

STEPS PER DAY

PARTICIPANTS WHO TOOK

≥8000

STEPS PER DAY,
compared with 4,000 steps per day, had significantly lower mortality from cancer (197).



LIMIT ALCOHOL CONSUMPTION

Drinking alcohol increases the risk for six different types of cancer (198) (see **Figure 9,** p. 48). Even modest use of alcohol may increase cancer risk, but the greatest risks are associated with excessive and/or long-term consumption (199–202) (see sidebar on **Guidelines for Alcohol Consumption,** p. 49). Researchers have identified multiple ways in which alcohol may increase the risk of cancer, including directly damaging cellular DNA and proteins through the production of toxic chemicals, once alcohol is metabolized after drinking (203). Alcohol can also increase levels of estrogen and other hormones that are associated with breast cancer (204). Several reports indicate that the use of alcohol has been rising in the U.S. in recent years (205–207). Concurrent with increases in consumption, rates of alcohol-related deaths have also increased at an alarming rate (208)(209).

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 (213), and in 2016, 4.2 percent of all cancer deaths globally were attributed to alcohol consumption (26). 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 focusing 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 cancer related to alcohol abuse. In this regard, several recent studies reported that when alcohol bottles contain conspicuous labels providing information on the risks of alcohol consumption and/or drinking guidelines, people are better informed about alcohol's adverse effects and may limit their drinking (214) (215).

PROTECT SKIN FROM UV EXPOSURE

All three main types of skin cancer—basal cell carcinoma, squamous cell carcinoma, and melanoma, the deadliest form of skin cancer—are largely caused by exposure to UV radiation from the sun or indoor tanning devices. In fact, more than 90 percent of the total cases of melanoma during 2011–2015 in the United States were attributable to UV exposure (216). Sunburn, a clear indication of overexposure to UV radiation, is a preventable risk factor for skin cancer and those events occurring in childhood pose the greatest risk (217). Therefore, one of the most effective ways a person can reduce 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. 50).

In the United States, melanoma incidence has been rising for decades among non-Hispanic whites (2)(218). To break this trend, multiple sectors including health care, the federal government, business, advocacy, and communities have coordinated efforts through public health campaigns, restrictive policies on tanning, and by encouraging sun-

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 (168).

For Preschool-Age Children (Ages 3–5)

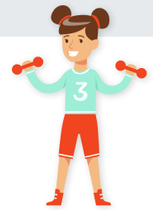
Physical activity throughout the day to enhance growth and development

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

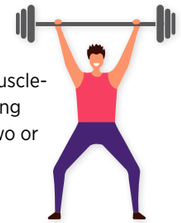


For Adults

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

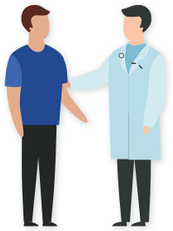
Moderate- or high-intensity muscle-strengthening activities two or more days per week



For specific populations

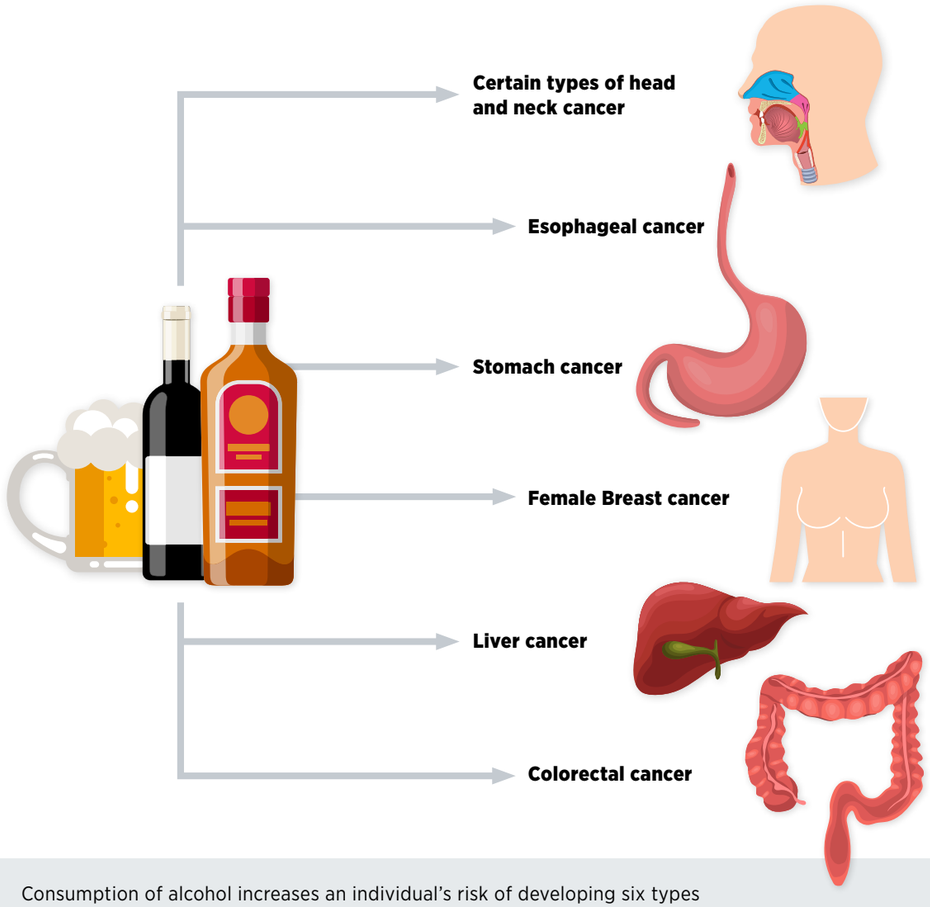
Older adults, those who are pregnant, and/or those with chronic health conditions and disabilities should consult their physicians and follow modified guidelines.

Cancer survivors should consult their physicians and follow modified guidelines adapted for their specific cancers and treatment.



Adapted from (1)

FIGURE 9 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.

protective behaviors to reduce melanoma risks. As a result, indoor tanning among U.S. youth and adults has declined significantly (219)(220) and early indications suggest that melanoma incidence is also beginning to decline among youth and young adults (ages 10 to 29 years), even though it continues to rise among those older than 40 (218)(221). Notably, even in 2015, more than 35 percent of adults reported experiencing sunburns, in the past year, either through outdoor exposure or indoor tanning (222). It is also concerning that even though 68 percent of Americans know that skin cancer is the most common cancer in the United States, only 42 percent put sunscreen on parts of their bodies exposed to the sun (223).

Continued efforts from all sectors are necessary to identify and implement more effective interventions to promote sun-safe behavior and reduce the burden of skin cancers. In this regard, a recent clinical trial that tested an intervention using a face-aging mobile app which altered "selfies" to show UV radiation's effects on an individual's future faces along with information about UV protection improved the skin cancer preventive behavior of high school students (224).

GUIDELINES FOR ALCOHOL CONSUMPTION

The U.S. Department of Health and Human Services and U.S. Department of Agriculture, *2015–2020 Dietary Guidelines for Americans,* recommends (181):

If alcohol is consumed, it should be done in moderation.

Moderate Drinking:

≤ 1 drink per day for women and **≤ 2 drinks per day** for men

and 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:

Heavy Drinking:

≥ 4 drinks on any day or ≥ 8 drinks per week for women and **≥ 5 drinks on any day or ≥ 15 drinks per week** for men

Binge Drinking:

≥ 4 drinks within 2 hours for women and **≥ 5 drinks within 2 hours** for men

Excessive alcohol consumption, which includes binge drinking, heavy drinking, and any drinking by pregnant women or those under 21 years of age, was responsible for an average of 93,296 deaths each year in the United States, during 2011 to 2015 (210).

The U.S. Preventive Services Task Force (USPSTF) recommends that clinicians screen adults age 18 and older for alcohol misuse and provide persons 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 (211).

Adapted from (212)

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 4**, p. 51). The primary causes of infection-attributable cancers are human papillomavirus (HPV), hepatitis B virus (HBV), hepatitis C virus (HCV), and *Helicobacter pylori* (110)(226)(227). In the United States, about 3 percent of all cancer cases are attributable to infection with pathogens while globally, an estimated 13 percent of all cancer cases are attributable to infections (110)(226). 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. 52). 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

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.

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

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

Adapted from (57)

BANNING INDOOR TANNING

Banning indoor tanning for all individuals ages 12 to 35 years in the United States and Canada can prevent

244,347
newly diagnosed melanomas and

89,193 deaths

from melanoma and save USD 3.5 billion in health care costs. Compared to the health and economic benefits of a ban just for minors, the benefits from such a broader restriction are more than 3 times higher (225).

strategies are not effective at treating infection-related cancers once they develop.

The annual rate of hepatitis C infection has tripled between 2009 and 2018, with infection rates highest among individuals ages 20 to 39 (228). Notably, only about 60 percent of HCV-positive individuals are aware of their status. Because of these alarming trends the CDC and the USPSTF recently updated their prior guidelines on HCV screening calling for universal screening at least once in their lifetime for all average-risk individuals age 18 and older (229)(230). The CDC also recommends pregnant women to be tested once during each pregnancy. People with continued risk, such as injection drug use, need to be screened regularly.

It is estimated that an average of 34,800 cancers reported annually in the United States during 2012–2016 were attributable to HPV infection (231). Notably, most of these cancers are caused by strains of HPV that are targeted by the vaccine Gardasil 9. HPV vaccines are highly effective and can prevent up to 90 percent of HPV-related cancers. Moreover, recent data indicate that in addition to directly protecting individuals who receive the vaccine, increased levels of vaccination may also promote herd immunity among the unvaccinated (232). Unfortunately, despite the multiple benefits, in 2019, only 57 percent of girls and 52 percent of boys were up to date with the recommended HPV vaccination regimen (121). While these numbers show slight improvement over earlier years, and there has also been some increase in uptake among young adults ages 18 to 26, vaccination rates in the United States are much lower than they are in other

TABLE 4 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

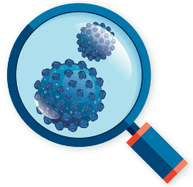
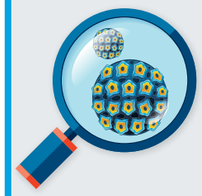
Pathogen	Cancer types caused by the pathogen	Number of global cancer cases
Epstein-Barr Virus (EBV)	Hodgkin lymphoma, certain types of non-Hodgkin lymphoma, and nasopharyngeal cancer	156,600
Hepatitis B Virus (HBV)	Hepatocellular carcinoma and other cancers	360,000
Hepatitis C Virus (HCV)	Hepatocellular 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 Ref https://www.thelancet.com/journals/langlo/article/PIIS2214-109X(19)30488-7/fulltext#seccestitle10

developed countries such as Australia where high vaccination rates (above 70 percent) are predicted to eliminate cervical cancer within the next 20 years (233)(234).

Until recently, cervical cancer was the most common HPV-related cancer in the United States. However, the incidence of HPV-related oropharyngeal and anal cancers has been increasing and oropharyngeal squamous cell carcinoma was recently reported to have become the most common HPV-associated cancer in the United States (237)(238). There are, however, no formal screening tests for oropharyngeal or anal cancers. Therefore, developing effective strategies to increase the uptake of HPV vaccines

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. 53**)

CDC, Centers for Disease Control and Prevention; MALT, mucosa-associated lymphoid tissue; USPSTF, U.S. Preventive Services Task Force.
Adapted from (57)

HPV VACCINATION RECOMMENDATIONS

13 **Thirteen strains of human papillomavirus (HPV) can cause cancer:** HPV16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 66.

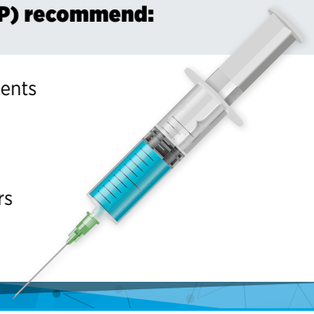
3 Although there are three FDA-approved HPV vaccines, only one (**Gardasil 9**) is currently being distributed in the United States.

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.

CDC **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.



could have immense public health benefits. In this regard, a recent study reported that protection provided by a single dose of the HPV vaccine is as durable as protection from the two-dose regimen (239). A single shot regimen can potentially improve vaccination rates and reduce health care and associated costs. Ongoing research is also needed to identify effective communications strategies that allow physicians to encourage HPV vaccination with successful implementation. It has been documented that an assertive rather than a passive approach by physicians while raising the issue of HPV vaccination with parents may increase vaccination in young adolescents, although recent reports indicate that some doctors do not follow this approach (240)(241). Another policy that may increase vaccination uptake is HPV immunization school-entry requirements. According to a recent report, three U.S. jurisdictions with such requirements had higher levels of vaccination initiation compared with jurisdictions in the same region without any requirements (242).

HPV VACCINATION AND CERVICAL SCREENING

In 2018, an estimated 570,000 cases of cervical cancer and 311,000 deaths from the disease occurred globally (235).

High coverage of HPV vaccination and cervical screening, globally, from 2020 onwards, could prevent nearly **13 million** cervical cancer cases over the next 50 years, and eliminate cervical cancer as a public health problem by 2099 (236).

BE COGNIZANT OF REPRODUCTIVE AND HORMONAL INFLUENCES

Breastfeeding

There is strong evidence that breastfeeding decreases the risk of breast cancer in the mother (243). Women who breastfeed have a lower risk of a particularly aggressive type of breast cancer known as triple-negative breast cancer (244). According to recent data (245), 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. 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 (246) (247). Increasing awareness of this information among African American women may be particularly important because African American women have a disproportionately high incidence of triple-negative breast cancer and a lower prevalence of breastfeeding compared with all other U.S. racial and ethnic groups (248).

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 due to declining 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 like 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.

The most comprehensive evidence about the health effects of HRT was obtained from clinical trials conducted by the NIH as part of the Women's Health Initiative. The data indicated that women who use estrogen plus progestin have an increased risk of developing breast cancer (249) (250). The risk is greater with longer duration of use (251) (252). 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 (252). Notably, the increased risks have been observed both for white and Black women (253) (254). Therefore, 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 in the United States (129). Other examples of environmental carcinogens include arsenic, asbestos, lead, radiation, and benzene. According to the World Health Organization (WHO), environmental risk factors account for nearly 20 percent of all cancers globally, most of which occur in low- and middle-income countries.

It is often 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, including genetic makeup, 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.

One environmental pollutant that was classified by the International Agency for Research on Cancer (IARC), an affiliate of the WHO, as having the ability to cause cancer in humans, is outdoor air pollution (255). 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 (256). Therefore, it is concerning that between 2016 and 2018, more than 21 million people in the United States were exposed year-round to unhealthy levels of particle pollution (256). New policy efforts to reduce the release of pollutants into the atmosphere are urgently needed to combat the adverse health effects of air pollution.

Involuntary exposures to environmental pollutants usually occur in subgroups of the population, such as workers in certain industries who may be exposed to carcinogens on the job 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 (257). 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, we need to develop and implement new and/or more effective policies that benefit everyone, including the most vulnerable and underserved populations.

EMERGING EVIDENCE ON CANCER RISK FACTORS

While epidemiological data highlight whether cancer risk factors can increase the risk of developing or dying from certain cancers, emerging mechanistic studies indicate how certain cancer risk factors such as obesity, smoking, and reproductive factors can influence disease subtype, aggressiveness, and outcomes through their effects on cancer cells and/or the tumor microenvironment including immune cells (258–261). Further research is needed to harness this knowledge for advancing cancer prevention and/or clinical management of disease. There is also accumulating evidence that suggest that beyond the well-established cancer risk factors, discussed above, there are several additional behavioral, social, as well as biological influences that may contribute to cancer development.

Psychosocial Stress

Stress-related social and behavioral factors have been considered as possible cancer risk factors. For example, it has been suggested that having a stress-prone personality and poor coping skills, as well as trauma-induced distress can affect incidence, mortality, and survival for various types of cancer (262–264). It is not clear whether the effects of stress-related psychological factors on cancer are due to an increase in risk-enhancing lifestyles, such as smoking, alcohol consumption, poor diet, and physical inactivity, or due to direct effects on our physiological systems. There is some evidence that stress can directly affect hormones and/or cellular processes including those that regulate our immune function, which in turn may contribute to cancer incidence or outcomes (262–267). One area of intensive research investigation is understanding the contribution of the allostatic load, which describes the combined influences of stresses, lifestyle, and environmental exposures, on the lifetime risk of cancer and other diseases (268)(269).

Metabolomics

The small molecules that are produced when our bodies break down food, drugs, chemicals, or our own tissue are known as metabolites. The process of breakdown, referred to as metabolism, produces the energy and materials that cells need to grow, reproduce, get rid of toxic substances, and stay healthy. Cancer development is associated with changes in the normal cellular metabolism, which provides the energy needed for uncontrolled cellular growth and division (270). Metabolomics is the study of metabolites in an individual's cells and tissues and is a measure of the "markers" of how well cells are functioning. Metabolites can be detected in the blood, urine, and other biospecimens. An individual's genetic makeup, lifestyle and environmental exposures such as diet and medications determine which metabolites are made and used in the body. Notably, emerging evidence suggests that certain metabolites may be associated with cancer development (271–276). However, more research is needed to evaluate whether the metabolite itself contributes to cancer development as opposed to factors that influence the metabolite levels (e.g., medication, environmental, or lifestyle factors). Definitive evidence on whether and which metabolites are associated with cancer risk will lead to more opportunities to develop preventive and/or therapeutic interventions against cancers.

SCREENING FOR EARLY DETECTION

IN THIS SECTION YOU WILL LEARN:

- Research identifying how cancer arises and progresses has led to the development of screening tests that can be used for early detection of cancer and precancerous lesions.
- There are five types of cancer (breast, cervical, colorectal, lung, and prostate) for which screening tests have been used to screen large segments of the U.S. 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.
- We need to develop new strategies to ensure optimal uptake of cancer screening by all individuals.

Research continues to increase our knowledge of the causes, timing, sequence, and frequency of the genetic, molecular, and cellular changes that drive cancer initiation and development (see **Understanding How Cancer Develops,** p. 19). This knowledge provides opportunities to develop screening tests that can find precancerous lesions or cancers at an early stage of development. It also provides insight into who is likely to benefit from screening and how often they should be screened.

WHAT IS CANCER SCREENING AND HOW IS IT DONE?

Screening for cancer means checking for precancerous lesions or cancer in people who have no signs or symptoms of the cancer for which they are being checked. The aim is to find an abnormality at the earliest possible time in cancer development. If a cancer screening test shows a precancerous lesion is present, it can be treated or surgically removed before becoming cancer (see **Figure 10,** p. 57). If a test finds a cancer at an early stage of development, stage I or stage II, before it has spread, it is more likely that the patient can be treated successfully; for example, patients diagnosed with colorectal cancer or breast cancer when the cancer is confined to the colon or rectum, or to the breast, have 5-year relative survival rates of 90 percent and 99 percent, respectively, while those diagnosed with colorectal cancer or breast cancer that has metastasized have 5-year relative survival rates of 14 percent and 28 percent, respectively (2). Treating or surgically removing a precancerous lesion or early-stage cancer is called cancer interception.

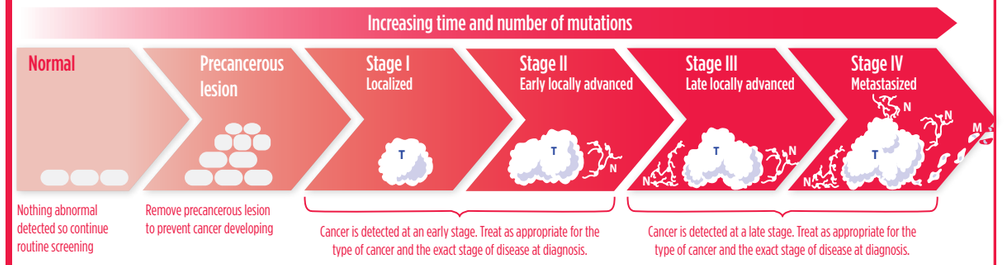
Screening for cancer can be done in various ways, including by using imaging technologies to look for abnormalities inside the body, and by collecting tissue or fluid samples and then analyzing them for abnormalities characteristic of the cancer being screened for (see sidebar on **How Can We Screen for Cancer?** p. 58). Currently, radiologists, pathologists, and other highly trained health care professionals interpret the images and/or the results of tissue or fluid sample analysis to determine whether an abnormality is present. This can be time consuming and can sometimes miss signs of cancer (false negative) or detect signs of cancer that turn out to be false positives. Researchers have been investigating for several years whether artificial intelligence (AI) approaches can enhance the interpretation of cancer screening tests. In the 12 months covered by this report, August 1, 2019, to July 31, 2020, the FDA has cleared for clinical use several AI systems to help radiologists detect breast cancer on mammograms (277). Many more AI approaches to improving the accuracy of screening mammography and other cancer screening tests are being studied, as discussed in **Looking to the Future** (p. 119) (278)(279).

Another area of research that is showing promise is the use of blood-based tests, or liquid biopsy tests, to screen for multiple types of cancer at the same time. Two research teams recently showed that this approach is feasible (280) (281), but more studies are needed before these tests can be used in the clinic for routine cancer screening (see **Looking to the Future** p. 119).

CONSENSUS ON CANCER SCREENING

Screening for cancer has many benefits, including reducing the likelihood of an individual being diagnosed with the screened cancer at an advanced stage and of dying from

FIGURE 10 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, 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), then it spreads to nearby lymph nodes (N), and, as it becomes more advanced, ultimately it metastasizes (M). When a person is screened for a given cancer, there are several different things that can be found, and different outcomes predicted based on the finding. For example, the screening test may show that there is no abnormality present; in this situation, the person should continue routine screening. The test may detect a precancerous lesion, which can be removed or treated; in this situation, the screen has led to the prevention of a cancerous lesion developing. The test may find a cancer at an early stage of development, stage I or stage II, before it has spread and at a point at which it is more likely that the patient can be treated successfully and have a higher likelihood of survival. It also may find a cancer at a late stage of development, stage III or stage IV, when treatment is less likely to be curative. Treating or surgically removing a precancerous lesion or treating early-stage cancer is called cancer interception.

Adapted from (57)

the screened cancer (see sidebar on **Cancer Screening,** p. 59). For example, recent data have shown that women who participated in mammography screening were 25 percent less likely to be diagnosed with advanced breast cancer and 41 percent less likely to be diagnosed with breast cancer that they would die from within 10 years of the diagnosis (282). However, screening for cancer also has the potential to cause unintended harms, which is why it is not recommended for everyone. Determining whether and for whom a cancer screening test can provide benefits that outweigh the potential harms requires extensive research and careful analysis of the data generated.

In the United States, an independent group of experts convened by the Agency for Healthcare Research and Quality of the 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 the U.S. Preventive Services Task Force (USPSTF).

The evidence-based USPSTF recommendations about 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, the USPSTF reevaluates existing recommendations as new research becomes available and can revise the recommendations if necessary. For example, the USPSTF is in the process of reviewing its recommendations for colorectal cancer

HOW CAN WE SCREEN FOR CANCER?

Highlighted here are some of the most commonly used cancer screening tests. When to use these tests and in whom is discussed elsewhere (see **Consensus on Cancer Screening p. 56**).

Breast Cancer

Screening mammogram:
Uses X-rays to image the breast.

The information generated by the procedure can be stored on film (a conventional mammogram) or electronically (a digital mammogram).

In most cases, the image is 2-dimensional, but some machines generate 3-dimensional images in a process called breast tomosynthesis.

Can detect breast cancers at any stage of development, but the aim of screening is to find them at the earliest possible stage.

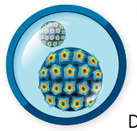
Breast magnetic resonance imaging (MRI): Uses radio waves and a powerful magnet linked to a computer to create a detailed image of the breast.

Can detect breast cancers at any stage of development, but the aim of screening is to find them at the earliest possible stage.

Cervical Cancer

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

Can detect precancerous or cancerous cervical lesions, but the aim of screening is to find them at the earliest possible stage.



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.

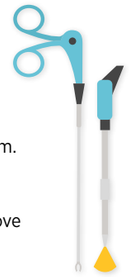
Prostate Cancer

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

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.

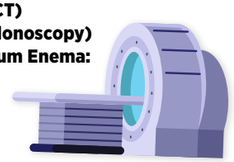
Do not directly detect colorectal precancerous lesions or cancers, but identify people for whom further testing is recommended.



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.

Can detect colorectal precancerous lesions or cancers at any stage; the aim of screening is to find and remove them before cancer develops.

Computed Tomography (CT) Colonography (Virtual Colonoscopy) and Double-Contrast Barium Enema:
Use X-rays to image the colon and rectum.



Can detect colorectal precancerous lesions or cancers, but the aim of screening is to find them at the earliest possible stage.

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.

Lung Cancer

Low-dose CT scan: Uses low doses of X-rays to image the lungs.

Can detect lung cancers at any stage of development, but the aim of screening is to find them at the earliest possible stage.

Adapted from (57)

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 10, p. 57**).

Reduced cancer mortality Diagnosis at an early stage of disease can increase the likelihood that a patient can be successfully treated, which thereby reduces the individual's risk of dying from the screened cancer.

Reduced incidence of advanced disease Screening tests that detect cancers at an early stage of development can reduce the individual's risk of being diagnosed with the screened cancer at a stage when it has spread to other parts of the body (see **Figure 10, p. 57**).

Potential Harms of Screening

Adverse events Screening tests are medical procedures; thus, they carry some risk. However, the chance that an adverse event will occur during a screening test recommended by the U.S. Preventive Services Task Force or a professional society is low.

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

False-positive test results Not all individuals who have a positive screening test result have the screened cancer. The rates of false-positive test results vary depending on the test but are generally low; a false-positive test result can result in additional unnecessary medical procedures, treatments, and anxiety.

False-negative test results Not all individuals who have a negative screening test result are free from the screened cancer. The rates of false-negative test results are generally low, but a false-negative test result can lead to missed opportunities for early treatment.

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. More longitudinal studies to elucidate and quantify the impact of overdiagnosis and overtreatment are required. Additional research is also needed to determine ways to identify which of the early-stage cancers detected through screening are most likely to go on to cause symptoms and threaten life.

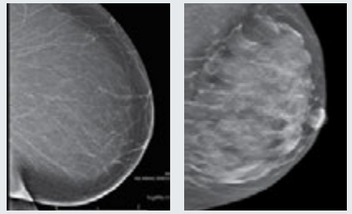
Adapted from (1)

screening. In light of accumulating evidence that the colorectal cancer incidence rate is rising among people age 49 and younger (24), one question being reviewed by the USPSTF is whether to lower the age it recommends for beginning colorectal cancer screening (see **The Growing Population Burden of Cancer,** p. 14).

A number of 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. Because the representatives on each panel are often different, and different groups give more weighting to certain

BREAST DENSITY

What Is Breast Density?



Nondense breast

Dense breast

Breast density refers to the appearance of a woman's breast on a mammogram. The more fibrous and glandular tissue in the breast and the less fat, the denser it appears on a mammogram. Radiologists—the physicians who interpret mammograms—classify breast density using four Breast Imaging Reporting and Data System (BI-RADS) breast density categories:

- Breasts are almost entirely fatty;
- There are scattered areas of dense fibrous and glandular tissue;
- There are more areas of dense fibrous and glandular tissue, making the breasts heterogeneously dense; and
- The breasts are extremely dense.

The last two categories are considered dense breasts.

Why Is Breast Density Important?

About 40 percent of women in their forties have dense breasts.

Women who have extremely dense breasts have a higher risk of developing breast cancer compared with women with less dense breast tissue. However, having extremely dense breasts is just one risk factor for breast cancer, and researchers are working to incorporate this factor into risk prediction models to help better determine a woman's risk for the disease.

Because dense breast tissue and breast cancers both look white on mammograms, dense breast tissue can make it harder to see breast cancer on a mammogram. Thus, dense breast tissue can reduce the effectiveness of mammograms.

Many U.S. states have enacted legislation mandating that women who have a mammogram be informed about breast density in general or about whether they have dense breasts. However, there currently is no consensus about what other breast cancer screening tests, if any, women with dense breasts should get in addition to mammograms. Thus, a woman informed that she has dense breasts should talk to her health care provider about whether additional testing with breast tomosynthesis, ultrasound, or magnetic resonance imaging is right for her.

Adapted from (212)

benefits and potential harms than other groups do, this can result in differences in recommendations from distinct groups of experts. For example, for breast cancer screening, there is a difference of opinion regarding whether screening should be done every year or every other year and whether regular screening should begin at age 40, age 45, or age 50.

Differences among cancer screening recommendations from different groups of experts highlight areas in which additional research is needed to determine more clearly the relative benefits and potential harms of screening, to develop new screening tests that have clearer benefits and/or lower potential harms, or to better identify people for whom the benefits of screening outweigh the potential harms.

Even though there is some variability among the recommendations from different groups of experts about the use of the screening tests for the five types of cancers for which screening is most commonly conducted, overall there is more consensus than disagreement (see sidebar on **Consensus Cancer Screening Recommendations,** p. 62). Nevertheless, it can still be challenging for individuals to ascertain for which cancers to be screened for and when. One of the most important factors people should consider when making decisions about cancer screening is their risk of the cancer being screened for. Recommendations for individuals at average risk of developing a certain cancer are different from those for individuals at increased risk of developing the same cancer. Each person has his or her own unique cancer risks; therefore, people should consult with their health care providers to develop cancer screening plans that are tailored to their own risks and tolerance for the potential harms of a screening test.

For individuals at average risk of developing a cancer for which there is a screening test, age and gender are the two main characteristics used to identify those for whom screening is recommended. Age is important because cancer is predominantly a disease of aging—91 percent of U.S. cancer diagnoses occur among those age 45 and older (2). Given that a person's risk for most types of cancer increases with age, it is important that individuals keep up a dialog with their health care providers and continually evaluate their cancer screening plans, updating them if necessary.

Some individuals have an increased risk of developing a certain type or types of cancer. Among the many reasons that a person might have an increased risk is through exposure to a cancer risk factor or cancer risk factors (see **Preventing Cancer: Identifying Risk Factors,** p. 37). For example, people who smoke cigarettes are about 25 times more likely to develop lung cancer than people who do not smoke cigarettes (8). Another reason is that an individual's unique cellular and tissue makeup might increase the risk of developing a certain type or types of cancer. For example, women who have extremely dense breasts have a higher risk of developing breast cancer compared with women with less dense breasts (284) (see sidebar on **Breast Density,** p. 60). Yet another reason that an individual might have an increased risk of developing a certain type or types of cancer is that he or she inherited a cancer-predisposing genetic mutation (see **Table 2,** p. 19).

If a person thinks that he or she is at high risk for inheriting a cancer-predisposing genetic mutation, the person should consult a health care provider and consider genetic testing (see sidebar on **How Do I Know If I Am at High Risk for Developing an Inherited Cancer?** p. 61). As researchers learn more about inherited cancer risk (285–288), there will be new genetic mutations to test for and changes to the recommendations about who should be offered genetic testing. For example, the USPSTF recently revised its recommendations on risk assessment, genetic counseling, and genetic testing for cancer related to BRCA1 or BRCA2 mutations in women, expanding the group that it recommends be screened for risk from only women who have family members with breast, ovarian, tubal, or peritoneal cancer to women with a personal or family history of breast, ovarian, tubal, or peritoneal cancer or an ancestry associated with BRCA1 or BRCA2 mutations (289). In addition, a group of prostate cancer experts recently recommended that men with a family history suggestive of hereditary prostate cancer should undergo testing for inherited mutations in the BRCA2 and HOXB13 genes and consider testing for inherited mutations in a larger panel of genes, including BRCA1, so as to gain information to help develop a prostate cancer screening plan tailored to the man's genetic makeup (290).

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

According to the National Cancer Institute, the features of an individual's personal or family medical history that, particularly in combination, may suggest an increased risk for developing an inherited cancer include (293):

- cancer diagnosed at a younger age than usual, such as colon cancer in a 20-year-old;
- more than one type of cancer 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 eyes, both kidneys, or both breasts;
- 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;
- unusual cases of a certain type of cancer, such as breast cancer in a man;
- the presence of birth defects associated with inherited cancer syndromes (see **Table 2, p. 23**), such as benign tumors associated with neurofibromatosis type 1;
- being a member of a racial or ethnic group known to have an increased risk of certain inherited cancer susceptibility syndromes and having one or more of the above features as well;
- several family members with cancer.

CONSENSUS CANCER SCREENING RECOMMENDATIONS

The U.S. government 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, 2020, among these recommendations from the U.S. government's U.S. Preventive Services Task Force (USPSTF), the American Cancer Society (ACS), the National Comprehensive Cancer Network (NCCN), the American College of Physicians (ACP), the American College of Obstetrics and Gynecology (ACOG), the American Urologists Association (AUA), and the United States Multi-Society Task Force (MSTF) on colorectal cancer. Not all the professional societies and organizations have recommendations for every cancer screening test.

Breast Cancer Screening

There is consensus among the ACOG, ACP, ACS, 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 recommend women at average risk for developing breast cancer begin regular screening mammograms at either age 40 or age 45. 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.

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 recently recommended raising the age at which women at average risk for cervical cancer begin screening from 21 to 25 (283).

Prostate Cancer

There is consensus among the 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.

Given that our knowledge of inherited cancer risk is continually increasing, it is important that individuals maintain an ongoing dialog with their health care provider and continually evaluate whether genetic testing is available and/or right for them. African American women are more likely to be diagnosed with breast cancer at a younger age than white women and are more likely to be diagnosed with biologically aggressive forms of the disease at all ages. Therefore, one area of intensive research investigation is whether disparities in breast cancer outcomes for African American women can be eliminated by changing the recommendations for genetic testing based on race and/

CONSENSUS CANCER SCREENING RECOMMENDATIONS *(CONTINUED)*

Colorectal Cancer Screening*

There is consensus among the ACS, ACP, NCCN, and USPSTF that adults ages 50 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. 58**).

Some professional societies and organizations, including the ACS, recommend starting regular screening at age 45 and some 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. 58**). For example:

- NCCN and MSTP on colorectal cancer recommend that individuals at increased risk because they inherited a genetic mutation that causes Lynch syndrome (see **Table 2, p. 23**) 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;
- ACS, NCCN, and MSTP 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,
- MSTP on colorectal cancer recommends that because African Americans are at increased risk for colorectal cancer, they should begin screening at age 45.

*USPSTF colorectal cancer screening guidelines are currently under review. Some of the issues being reviewed are whether screening should begin at an earlier age for all average-risk individuals and whether recommendations should vary by race and/or ethnicity.

Lung Cancer*

There is consensus among the ACS, NCCN, and USPSTF that annual screening with low-dose computed tomography should be limited to adults ages 55 to 80 who are at high risk for lung cancer because they have smoked at least one pack of cigarettes per day for 30 years, or the equivalent (two packs per day for 15 years, etc.), and who currently smoke or have quit within the past 15 years.

*USPSTF lung cancer screening guidelines are currently under review. Some of the issues being reviewed are whether screening should begin at an earlier age and include individuals who have smoked cigarettes for less than 30 pack years.

Adapted from (57)

or ethnicity and by ensuring that those African American women for whom genetic testing is currently recommended undergo testing (291)(292).

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

All individuals who have an increased risk of developing a certain type or types of cancer should consult with their

TABLE 5 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

health care providers to tailor risk-reducing measures to their personal situation. Some may be able to reduce their risk by modifying their behaviors, for example, by quitting smoking. Others might need to increase their use of certain cancer screening tests or use cancer screening tests that are not recommended for people who are at average risk for the cancer. Yet others may consider taking a preventive medicine or having risk-reducing surgery (see **Table 5,** p. 64, and **Supplemental Table 1,** p. 164).

As we increase our understanding of the biology of precancerous and cancerous lesions we will be able to better tailor cancer prevention and early detection to the individual patient, ushering in a new era of precision cancer prevention (294)(295). One area of interest is whether screening guidelines should differ for individuals from different racial and ethnic minority groups. For example, researchers have suggested that lung cancer screening recommendations may need to be less stringent for African Americans after it was shown that African American men have an increased risk of lung cancer despite lower pack years of smoking (296). Another area of intensive research investigation is whether cancer screening should be tailored depending on the density of a woman's breasts because women who have dense breasts have a higher risk of developing breast cancer compared with those who have less dense breasts. Early data suggest that using magnetic resonance imaging (MRI) rather than mammography or using both MRI and mammography may increase the detection of invasive breast cancer during screening of women with dense breasts (297) (298), but whether this translates to reductions in deaths from breast cancer has yet to be determined. Survivors of cancer diagnosed in childhood or adolescence are another group who require carefully tailored cancer prevention and early detection plans because they are at increased risk of developing another type of cancer in adulthood and cancer is a leading cause of death among this group (299)(300) (see **Supporting Cancer Patients and Survivors,** p. 111).

SUBOPTIMAL USE OF CANCER SCREENING TESTS

Even though the benefits of screening for breast, cervical, colorectal, and lung cancer outweigh the potential risks for defined groups of individuals (see sidebar on **Consensus Cancer Screening Recommendations,** p. 62), many of those for whom screening is recommended do not get screened (see sidebar on **Use of Cancer Screening Tests is Suboptimal,** p. 65). 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. 66).

In addition to suboptimal uptake among those individuals for whom screening is recommended, some people for whom screening is not recommended, such as individuals below or above the recommended age range for a given cancer screening test and 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 (304–306).

The suboptimal use of cancer screening tests and the significant disparities in cancer screening rates among

USE OF CANCER SCREENING TESTS IS SUBOPTIMAL

Not all people for whom cancer screening is recommended are up to date with screening (see sidebar on **Consensus Cancer Screening Recommendations, p. 62**). For example, a substantial percentage of individuals for whom the U.S. Preventive Services Task Force recommended breast, cervical, colorectal, or lung cancer screening were not up to date with screening at last assessment:

28.5% 28.5 percent of women ages 50–74 were not up to date with breast cancer screening in 2015 (301).

17% 17 percent of women ages 21–65 were not up to date with cervical cancer screening in 2015 (301).

31% 31 percent of adults ages 50–75 were not up to date with colorectal cancer screening in 2018 (302).

87% 87 percent of adults ages 55–80 who have smoked at least one pack of cigarettes per day for 30 years, or the equivalent (two packs per day for 15 years, etc.), and who currently smoke or have quit within the past 15 years were not up to date with lung cancer screening in 2017 (303).

certain segments of the U.S. population highlight the need for new strategies and public policies to increase cancer screening awareness, access, and uptake among those for whom screening is recommended. Actively reaching out and providing individuals with culturally sensitive information can help optimize use of cancer screening tests (307–310). This can be done in the form of mailing information to individuals, as exemplified by the reduction in the number of women above the USPSTF-recommended cut-off age for breast cancer screening—those age 75 and older—who underwent breast cancer screening after receiving a pamphlet about mammography before they visited their doctor (307). It can also be done through patient navigation programs that provide individualized assistance to help patients overcome personal and health care system barriers, and to facilitate understanding and timely access to screening (308–310). Another approach that has been shown to successfully increase colorectal and cervical cancer screening rates is to mail individuals a stool test or an HPV kit, respectively, that allows people to collect their own sample at home (309)(311).

Federal agencies and the federal government also have a role to play in optimizing cancer screening (see **Advancing Effective Cancer Prevention, Treatment, and Control Efforts,** p. 135). For example, the NCI and CDC support numerous programs that help provide resources, materials, and infrastructure for outreach and education, and that increase access and utilization of cancer screening services. In addition, the Affordable Care Act requires Marketplace plans to provide without cost-sharing colorectal cancer screening for adults ages 50 to 75, tobacco use screening, and lung cancer screening for adults ages 55 to 80 who are at high risk for lung cancer (www.healthcare.gov/preventive-care-adults/). Research suggests that by eliminating out-of-pocket costs for preventive colonoscopies, the Affordable Care Act has reduced disparities in colorectal cancer screening (312), but other approaches are needed to fully optimize the use of cancer screening tests.

DISPARITIES IN CANCER SCREENING

There are disparities in adherence to U.S. Preventive Services Task Force cancer screening recommendations among certain segments of the U.S. population. These disparities, which are a result of complex and interrelated factors (see sidebar **Why Do U.S. Cancer Health Disparities Exist? p. 17**), include the following (301) (302):

72% vs 57%	White women are significantly more likely to be up to date with breast cancer screening than American Indian/Alaska Native women, 72% versus 57%.
77% vs 58%	Adults in Massachusetts are significantly more likely to be up to date with colorectal cancer screening than those in Wyoming, 77% versus 58%.
83% vs 75%	Straight women are significantly more likely to be up to date with cervical cancer screening than lesbian or gay women, 83% versus 75%.
79% vs 59%	Women in the highest income bracket are significantly more likely to be up to date with breast cancer screening than women in the lowest income bracket, 79% versus 59%.
71% vs 40%	Adults who have health insurance are significantly more likely to be up to date with colorectal cancer screening than adults who are uninsured, 71% versus 40%.
85% vs 67%	Women who were born in the United States are significantly more likely than women who have lived in the United States for less than 10 years to be up to date with cervical cancer screening, 85% versus 67%.

TURNING SCIENCE INTO LIFESAVING CARE

IN THIS SECTION YOU WILL LEARN:

- Research that increases our understanding of the genetic, molecular, and cellular characteristics of cancer is continuing to spur advances in the treatment of cancer.
- Advances are being made across all five pillars of cancer care: surgery, radiotherapy, cytotoxic chemotherapy, molecularly targeted therapy, and immunotherapy.
- From August 1, 2019 to July 31, 2020, the FDA approved 20 new therapeutics for treating patients with certain types of cancer.
- During the same period, the uses of 15 previously approved anticancer therapeutics were expanded by the FDA to include the treatment of additional types of cancer.

Progress across the continuum of clinical cancer care improves survival and quality of life for people around the world. The progress is driven by the dedicated efforts of individuals working throughout the cycle of medical research (see **Figure 11,** p. 68).

MEDICAL RESEARCH

Medical research is an iterative process that is set in motion when a discovery with the potential to affect the practice of medicine or public health is made in any area of research or clinical practice (see **Figure 11**, p. 68). One way that researchers build on a discovery is by asking questions that can be tested through experiments in a wide range of models that mimic healthy and diseased conditions. Results from these experiments can lead to the identification of a potential preventive intervention or therapeutic target, or to the identification of a potential predictive or prognostic biomarker. They also can feed back into the cycle by providing new discoveries that lead to more questions or hypotheses.

If a potential therapeutic target is identified, it takes many more years of preclinical research before a candidate therapeutic is developed and ready for testing in clinical trials (see sidebar on **Therapeutic Development,** p. 69). During this time, several candidates are rigorously tested to identify any potential toxicity and to determine the appropriate doses and dosing schedules for testing in the first clinical trial.

There are many types of clinical trials, each designed to answer different research questions (see sidebar on **Types of Clinical Trials,** p. 70). All clinical trials are reviewed and approved by institutional review boards before they can begin and are monitored throughout their duration.

Clinical trials testing the safety and efficacy of candidate anticancer therapeutics have traditionally been done in three successive phases (see **Figure 12,** p. 71). However, this traditional approach requires a very large number of patients and takes many years to complete, making it extremely costly and one of the major barriers to rapid translation of scientific knowledge into clinical advances. Recent analyses have estimated that the median research and development cost for a new anticancer therapeutic or immune-system modulating therapeutic is $2.77 billion and that despite efforts to reduce the overall time, it still takes about eight years for an anticancer therapeutic to progress through clinical development and approval (313)(314).

Over the past few decades, the FDA has implemented several changes that have altered how clinical trials can be conducted and reviewed in an effort to reduce the length of time it takes to obtain a clear result from a clinical trial, including developing four evidence-based strategies to expedite assessment of therapeutics for life-threatening diseases such as cancer. New anticancer therapeutics are far more likely to undergo regulatory assessment using these expedited strategies than new therapeutics being tested in other fields of medicine, and this is associated with a 48 percent shorter regulatory review time for anticancer therapeutics (314).

In addition, advances in our understanding of cancer biology have enabled researchers, regulators, and the pharmaceutical industry to develop new ways to design and conduct clinical trials. The new designs, including adaptive, seamless, and master protocol designs, aim to streamline the clinical

FIGURE 11 THE MEDICAL RESEARCH CYCLE

Results from any type of research can fuel the medical research cycle by providing observations relevant to the practice of medicine, which lead to questions, or hypotheses, that are tested in experiments during the discovery phase of research. During the discovery phase, traits unique to a disease may be uncovered, leading to the development of a potential therapeutic (see sidebar on **Therapeutic Development,** p. 69). Before entering clinical testing, potential therapeutics undergo preclinical testing to identify any toxicities and help determine initial dosing. The safety and efficacy of potential therapeutics are then tested in clinical trials. If an agent is safe and efficacious, and it is approved for use by the U.S. Food and Drug Administration (FDA), it will enter clinical practice. Importantly, observations made during the routine use of a new therapeutic can feed back into the medical research cycle and further enhance the use of that agent or the development of others like it. If, however, a therapeutic is not safe or efficacious and fails to gain FDA approval, the observations from the clinical testing still feed back into the medical research cycle to spur future research efforts. Because the cycle is iterative, it is constantly building on prior knowledge, and research undertaken during any part of the cycle continually powers new observations.

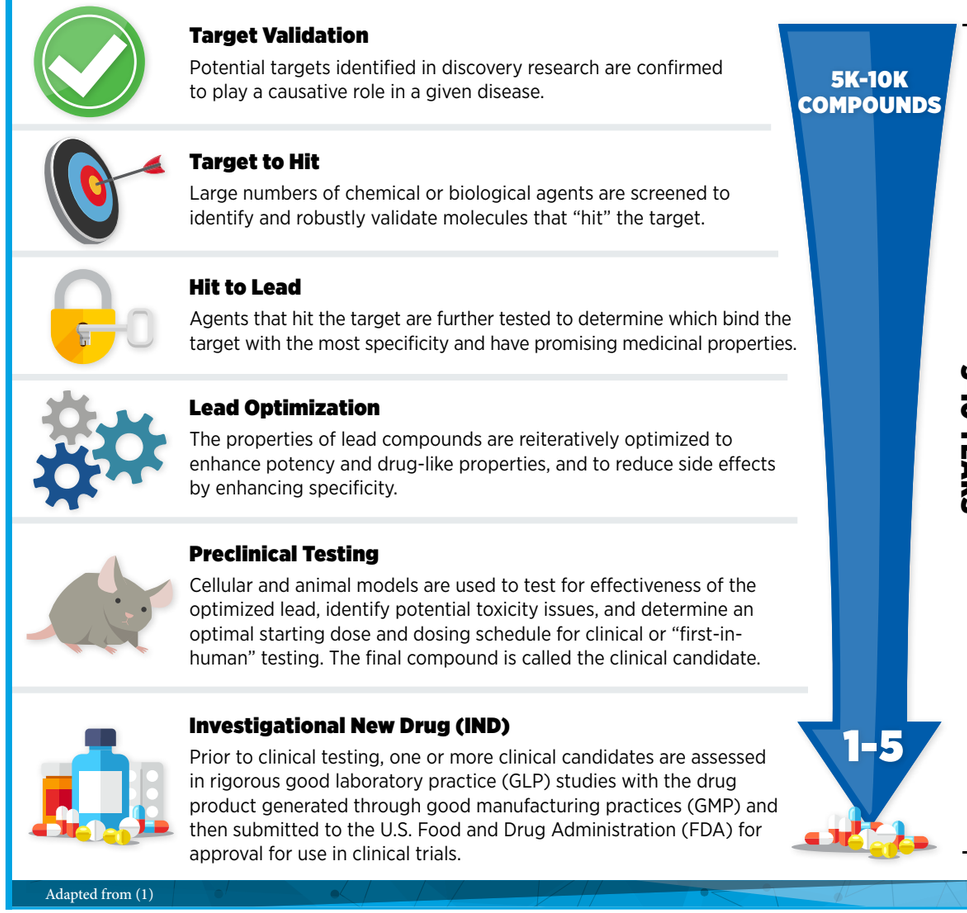
Figure adapted from (40)

development of new anticancer therapeutics by matching the right therapeutics with the right patients earlier, reducing the number of patients who need to be enrolled in the trial before it is determined whether the anticancer therapeutic being evaluated is safe and efficacious, and/or 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 efficacious (315–317).

Master protocol design clinical trials aim to answer multiple questions within a single overall clinical trial (317). The emergence of this clinical trial design has largely been driven by our increased understanding of the genetic mutations that promote cancer initiation and growth. "Basket" trials are one example of genetic mutation–based master protocol design clinical trials (see **Figure 13,** p. 72). These trials allow researchers to test one anticancer therapeutic on a group of patients who all have the same type of genetic mutation, regardless of the anatomic site of the original cancer, as highlighted in **Targeting an Array of Cancers That Share the Same Genetic Alteration,** p. 79).

Even though we have new ways of designing, conducting, and reviewing clinical trials that are yielding advances in patient care, there are still opportunities to improve the clinical trial enterprise. Some of the most pressing challenges that need to be overcome are low participation in clinical trials, in particular among individuals living in rural areas and adolescents and young adults, and a lack of representation from all populations among individuals of all ages who do participate (318–322) (see sidebar on **Disparities in Clinical Trial Participation,** p. 73). Overcoming barriers to clinical trial participation for all segments of the population will require all stakeholders in the cancer community to come together to develop a multifaceted approach that includes the development and implementation of new, more effective education and policy initiatives.

THERAPEUTIC DEVELOPMENT



Adapted from (1)

PROGRESS ACROSS THE SPECTRUM OF CANCER TREATMENT

Research discoveries that have been made as a result of innovative cancer science are continually being translated to new medical products for cancer prevention, detection, diagnosis, treatment, and survivorship. The approval of new medical products is not the end of a linear research process. Rather, it is an integral part of the medical research cycle because observations made during the routine use of new medical products can be used to accelerate the pace at which similar products are developed and to stimulate the development of new, more effective products.

The following discussion focuses primarily on medical products approved by the FDA in the 12 months spanning this report, August 1, 2019, to July 31, 2020. In particular, it focuses on the 20 new anticancer therapeutics approved by the FDA during this period (see **Table 6,** p. 74). Also highlighted are the 15 previously approved anticancer therapeutics that were approved by the FDA for treating additional types of cancer during that time. Not discussed are FDA approvals related to expanding the use of an anticancer therapeutic previously approved for a given type of cancer to include additional dosing regimens or additional uses during the treatment of the same cancer type; for example, an expansion to include treatment of the same type of cancer at a less advanced stage of disease.

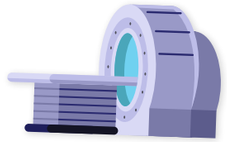
TYPES OF CLINICAL TRIALS

There are different types of clinical trials, each designed to answer different research questions. Many types of clinical trials are designed to find out more about a particular medical product or intervention, but some trials are observational in nature. In oncology, the types of clinical trials include:

Prevention Trials
are designed to find out whether healthy people can reduce their risk of cancer by taking certain actions, such as being more physically active; by taking certain therapeutics, vitamins, minerals, or dietary supplements; or by having certain risk-reducing surgeries.

Screening Trials
are designed to test whether new ways to detect a certain type of cancer early in development are effective at reducing deaths from the type of cancer being screened for.

Diagnostic Trials
are designed to test new ways to diagnose a certain type of cancer.

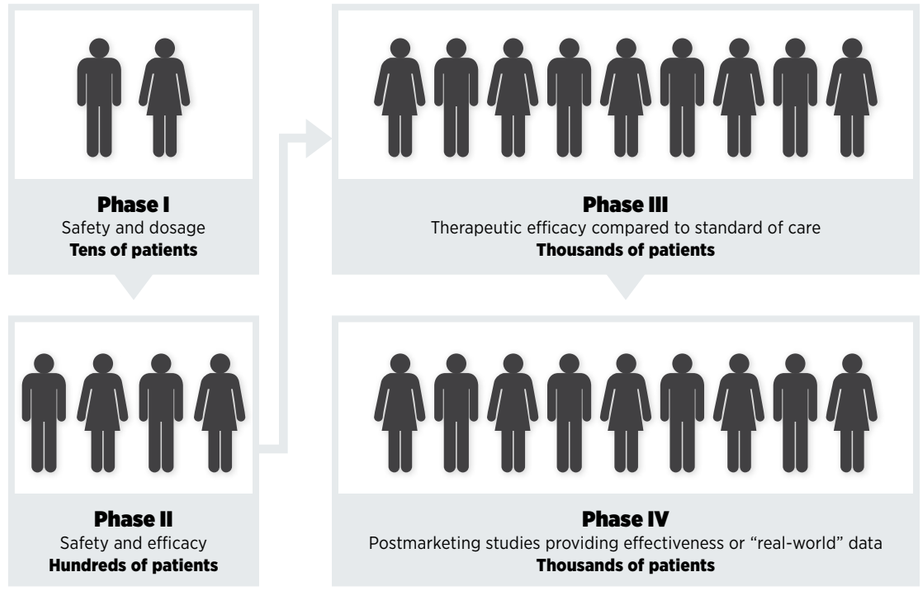


Treatment Trials
are designed to test whether new treatments or new ways of using existing treatments are safe and efficacious for people who have cancer. These trials can test any type of treatment, including surgery, radiotherapy, cytotoxic chemotherapy, molecularly targeted therapy, and immunotherapy, alone or in combination with another treatment(s).

Quality of Life Trials (also known as supportive care or palliative care trials)
are designed to find out whether people who have cancer can improve their quality of life by taking certain actions, such as attending support groups or being more physically active; or by taking certain therapeutics, such as those to treat depression or nausea.

Natural History or Observational Studies
are 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. Depending on the study, researchers may collect details about the participants' medical history; their families' medical histories; tissue (such as blood and saliva); tumor samples; information about the participants' lifestyle, such as how physically active they are or what they eat; or other information.

FIGURE 12 PHASES OF CLINICAL TRAILS



Clinical trials evaluating potential new therapeutics for treating patients with cancer have traditionally been done in three successive phases, each with an increasing number of patients. Phase I studies are designed to determine the optimal dose of an investigational anticancer therapeutic, how humans metabolize it, and the potential toxicities. Phase II studies are designed to determine the initial efficacy of an investigational therapy, in addition to continually monitoring for potential toxicities.

Phase III studies are large trials designed to determine therapeutic efficacy as compared with standard of care (placebos are rarely used in cancer clinical trials). 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 the FDA and provide additional effectiveness or "real-world" data on the therapy.

Adapted from (40)

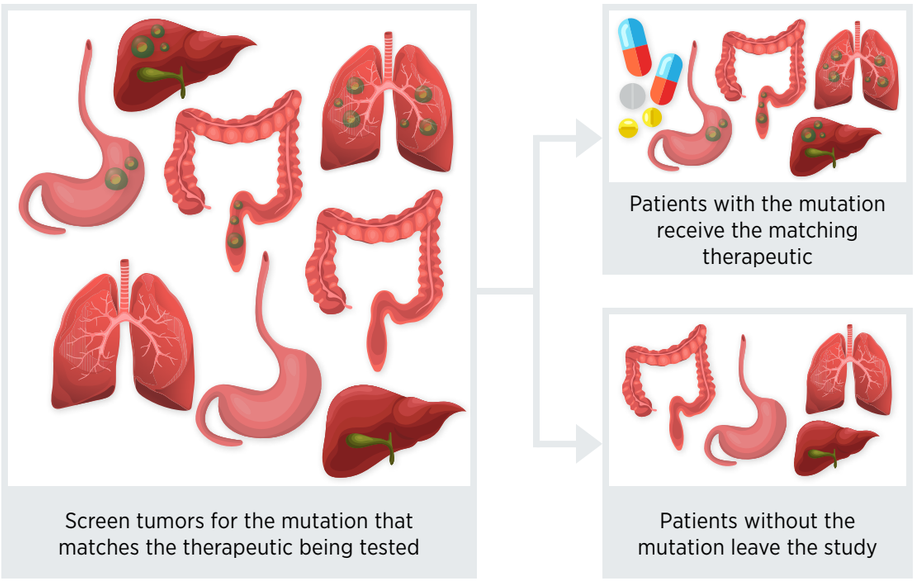
New FDA-approved medical products are usually used alongside treatments already in use, including surgery, radiotherapy, and cytotoxic chemotherapy, which continue to be vital pillars of clinical cancer care (see **Figure 14,** p. 75) (see **Supplemental Table 2,** p. 165, and **Supplemental Table 3,** p. 169). Despite the continual progress in cancer treatment, not all patients receive the care recommended for the type and stage of cancer with which they have been diagnosed (sidebar on **Disparities in Cancer Treatment,** p. 76). It is imperative that all stakeholders committed to accelerating the pace at which we make breakthroughs against cancer work together to address the challenge of disparities in cancer treatment because these can be associated with adverse differences in survival. In fact, recent research has shown that disparities in multiple myeloma and prostate cancer survival for African Americans compared with whites were eliminated if they had equivalent access to care and to standard treatments (323)(324).

Treatment with Surgery

Until the late 19th century, surgery was the only approach to treating patients with cancer (see **Figure 14,** p. 75). Today, it remains the foundation of treatment for many patients (330) (see sidebar on **Using Surgery in Cancer Care,** p. 77).

FIGURE 13 MASTERING CLINICAL TRIAL DESIGN

Basket Trials



Recent advances in our understanding of cancer biology have led to new ways of designing and conducting clinical trials. One of the new approaches is to use a master protocol to answer multiple questions within a single overall clinical trial. Basket trials are one type of master protocol clinical trial. In the basket trial depicted here, one drug is being tested against a particular genetic mutation (green dots) across liver, lung, colon, and stomach cancers. This approach allows the clinical testing of new anticancer therapeutics to be streamlined because the therapeutic is matched with the right patients at the start of the trial. This precision approach reduces the number of patients who need to be enrolled in the trial before it is determined whether or not the anticancer therapeutic being evaluated is safe and effective, and/or decreases the length of time it takes for a new anticancer therapeutic to be tested and made available to patients if the trial shows it is safe and effective.

Adapted from (112)

Adding Therapy before Surgery

For some patients with cancer, surgery alone may be the best treatment option. However, other patients are treated with radiotherapy, cytotoxic chemotherapy, molecularly targeted therapy, and/or immunotherapy before surgery, a treatment approach called neoadjuvant therapy. Neoadjuvant therapy can be used to shrink a large tumor so that the surgery performed is less invasive, less complicated, and/or more likely to be curative. It can also be used to shrink a tumor that cannot be removed surgically because it is too large or too close to an important organ or tissue, so that it can be removed surgically.

Researchers are continually investigating ways to increase the number of patients who benefit from neoadjuvant therapy and, thereby, hone the use of surgery in cancer treatment. For example, recent data showed that neoadjuvant cytotoxic chemotherapy has the potential to increase the number of patients with pancreatic cancer who are eligible for surgery. In two early-stage clinical trials, this treatment led to a significant proportion of patients with locally advanced pancreatic cancer that could not be removed by surgery going on to have the cancer fully removed surgically, and this was associated with improved survival (331) (332).

Many patients with stage III melanoma are treated with surgery. Unfortunately, even if the surgery is successful, these individuals are at high risk of the melanoma recurring (333) (334). Therefore, researchers are investigating whether neoadjuvant therapy can improve the chances of surgery being curative for stage III melanoma. In one study, neoadjuvant therapy with a combination of the molecularly targeted therapeutics dabrafenib (Tafinlar) and trametinib (Mekinist) was shown to make it easier for the tumor and surrounding tissue to be surgically removed in almost half of patients (333). It also shrank tumors for most patients, as did a combination of immunotherapeutics—ipilimumab (Yervoy) and nivolumab (Opdivo)—in another clinical trial (334). Longer follow-up of the patients in both trials is needed to determine whether these neoadjuvant therapies ultimately reduce risk of relapse and improve cure rates.

Reducing the Need for a Second Surgery

Despite the immense benefits of surgery, complications can occur and can negatively affect a patient's quality of life. One recent advance may help women with breast cancer who choose to have breast-conserving surgery avoid the challenge of needing a second surgery to provide the best chance of a cure (335). It is estimated that about 50 percent of women who are diagnosed with breast cancer have breast-conserving surgery—surgery to remove a breast tumor and a small amount of normal tissue around it that leaves most of the breast skin and tissue in place. However, more than 20 percent of patients require a second surgery, known as re-excision, because postsurgery analysis of the removed tumor shows an inadequate margin of normal tissue around the tumor, leaving open the possibility that not all the tumor was removed. A recent study showed that using 3-dimensional breast tomosynthesis in the operating room to guide the surgery reduced the rate of re-excision by more than 50 percent compared with using standard 2-dimensional breast imaging (336).

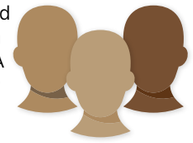
Using Surgery to Treat Metastatic Cancer

Traditionally, the main use of surgery in the treatment of patients with metastatic cancer has been to reduce or control problems caused by the cancer, such as pain, pressure, and blockages. However, recent research suggests that surgery can benefit patients with some types of cancer who have metastatic tumors at a limited number of sites and are said to have oligometastatic disease (337)(338). For example, although soft tissue sarcoma metastases often recur after surgical removal, it is possible to perform serial surgeries that allow patients who have oligometastases to live disease

DISPARITIES IN CLINICAL TRIAL PARTICIPATION

If we are to ensure that candidate anticancer therapeutics are safe and effective for everyone who will use them if they are approved, it is vital that the participants in the clinical trials testing the agents represent the diversity of the patient population. Despite this knowledge, several segments of the population have been found to be underrepresented in clinical trials relative to their levels in the general census and/or the relevant disease populations. Examples of these disparities include the following:

African Americans and Hispanics accounted for 3.1 percent and 6.1 percent of participants in clinical trials supporting FDA approvals of new anticancer therapeutics from July 2008 to June 2018, which is just 22 percent and 44 percent of what would be expected based on the proportion of individuals from these minority groups among U.S. adults who have cancer (320).



Patients with cancer who have an annual household income of <$50,000 are 32 percent less likely to participate in a clinical trial than patients who have a higher income (321).

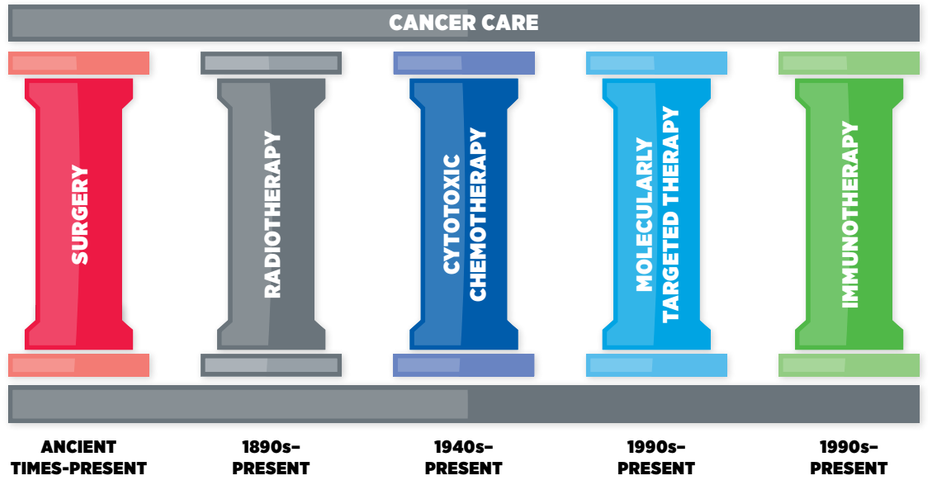
Less than 2 percent of adolescents and young adults (ages 15 to 39) with cancer enroll in treatment clinical trials compared with about 60 percent of patients younger than 15 (322).

TABLE 6 NEWLY FDA-APPROVED ANTICANCER THERAPEUTICS: AUGUST 1, 2019–JULY 31, 2020

Approved Indication	Generic Name	Trade Name
CAR T-cell Therapy		
Certain type of non-Hodgkin lymphoma	brexucabtagene autoleucel	Tecartus
Cell-signaling Inhibitors		
Certain types of leukemia and lymphoma†	acalabrutinib	Calquence
Certain type of gastrointestinal stromal tumor	avapritinib*	Ayvakit
Certain type of lung cancer	capmatinib*	Tabrecta
Certain type of colorectal cancer†	encorafenib* and cetuximab	Braftovi and Erbitux
Certain type of bladder cancer	enfortumab vedotin-ejfv	Padcev
NTRK-positive solid tumors and certain lung cancers	entrectinib	Rozlytrek
Certain type of myeloproliferative neoplasm	fedratinib	Inrebic
Certain type of breast cancer	fam-trastuzumab deruxtecan-nxki	Enhertu
Certain type of bile duct cancer	pemigatinib*	Pemazyre
Tenosynovial giant cell tumor	pexidartinib	Turalio
Gastrointestinal stromal tumor	ripretinib	Qinlock
Certain type of breast cancer	sacituzumab govitecan-hziy	Trodelvy
Certain types of lung and thyroid cancer	selpercatinib	Retemvo
Neurofibromatosis type 1	selumetinib	Koselugo
Certain type of breast cancer	tucatinib	Tukysa
Certain type of non-Hodgkin lymphoma	zanubrutinib	Brukinsa
Cell Lysis Mediators		
Multiple myeloma	isatuximab-irfc	Sarclisa
Certain type of non-Hodgkin lymphoma	tafasitamab-cxix	Monjuvi
DNA-damaging Agents		
Certain type of bladder and kidney cancer†	mitomycin	Jelmyto
DNA-repair Inhibitors		
Certain types of pancreatic† and prostate cancer†	olaparib*	Lynparza
Certain type of prostate cancer†	rucaparib*	Rubraca
Epigenome-modifying Agent		
Certain types of blood cancer	decitabine and cedazuridine	Inqovi
Certain types of sarcoma and lymphoma†	tazemetostat	Tazverik
Gene-transcription Modifier		
Certain type of lung cancer	lurbinectidin	Zepzelca
Immune-checkpoint Inhibitors		
Certain types of liver† and lung cancer†	ipilimumab and nivolumab	Yervoy and Opdivo
Certain type of lung cancer†	durvalumab	Imfinzi
Certain type of esophageal cancer†	nivolumab	Opdivo
Certain types of skin† and colorectal† cancers and solid tumors that are TMB-H†	pembrolizumab*	Keytruda
Immune-system Modifiers		
Kaposi sarcoma†	pomalidomide	Pomalyst
Nuclear Export Inhibitor		
Certain type of lymphoma†	selinexor	Xpovio
Combinations of Therapeutics That Work in Different Ways		
Certain type of liver cancer†	atezolizumab and bevacizumab	Tecentriq and Avastin
Melanoma†	atezolizumab and cobimetinib and vemurafenib	Tecenriq and Cotellic and Zelboraf
Endometrial cancer†	pembrolizumab and lenvatinib	Keytruda and Lenvima

†new cancer type approved 2019–2020 * requires a companion diagnostic

FIGURE 14 THE PILLARS OF CANCER CARE



Physicians often refer to the "pillars" of cancer treatment. For many years, there was one treatment pillar: surgery. In 1896, a second pillar, radiotherapy, was added. The foundations for the third treatment pillar, cytotoxic chemotherapy, were laid in the early 1940s when a derivative of nitrogen mustard was explored as a treatment for lymphoma. These three pillars—surgery, radiotherapy, and cytotoxic chemotherapy—continue to be critical components of cancer care. The first molecularly targeted therapeutics were introduced in the late 1990s, leading to the fourth pillar, molecularly targeted therapy. Likewise, the late 1990s laid the groundwork for the fifth treatment pillar, immunotherapy. The number of anticancer therapeutics that form the most recent two pillars of cancer care continues to increase every year.

Adapted from (36)

free for periods of time (337). For patients with lung cancer who have oligometastases, surgical removal of the initial lung tumor and oligometastases combined with other approaches to treatment can improve survival, and for patients with colorectal cancer who have a limited number of metastases in the liver, radiofrequency ablation combined with surgery can improve survival (338)(339).

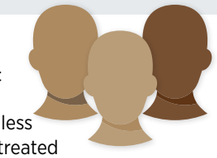
Treatment with Radiotherapy

Radiotherapy became the second pillar of cancer treatment in 1896 (see **Figure 14,** p. 75). Today, about 50 percent of patients receive radiotherapy to shrink or eliminate tumors or to prevent local recurrence (330) (see sidebar on **Using Radiation in Cancer Care,** p. 78).

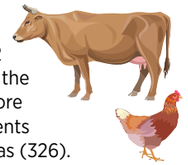
Traditionally, the main use of radiotherapy in the treatment of patients with metastatic cancer was to reduce or control symptoms of disease. This is beginning to change as a result of advances in radiotherapy and emerging evidence that up to 50 percent of patients diagnosed with metastatic cancer have oligometastatic disease, meaning there are metastatic tumors at a limited number of sites. Stereotactic ablative radiotherapy is an advanced approach to radiotherapy that can more precisely target radiation to tumors than conventional forms of external beam radiotherapy. The high degree of precision means that higher doses of radiation can be used and that healthy tissues surrounding a tumor are spared from damage caused by the radiation, which can reduce the long-term adverse effects of radiotherapy. Recent clinical trials have shown that stereotactic ablative radiotherapy targeted to oligometastatic tumors can reduce the chances of disease progression and increase survival for patients who have solid tumors, such as prostate cancer, lung cancer, and gastrointestinal tumors (340–343). In

DISPARITIES IN CANCER TREATMENT

Research is constantly powering the development of new cancer treatments. However, several segments of the population have been found to be disproportionately less likely to receive recommended cancer treatments. Examples of these disparities include:



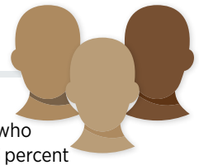
Patients with localized, nonmetastatic pancreatic cancer who are African American are 24 percent less likely to have the cancer treated with surgery compared with whites (325).



Patients with rectal cancer who live in rural areas are 42 percent less likely to receive the recommended radiation before surgery compared with patients who live in metropolitan areas (326).

Patients with early-stage non–small cell lung cancer who lack health insurance are 46 percent less likely to receive standard postsurgery radiotherapy and/or chemotherapy compared with those who have private health insurance (327).

Patients with multiple myeloma who are African American are 31 percent less likely to receive the molecularly targeted therapeutic bortezomib (Velcade) compared with those who are white (328).



Patients with metastatic non–small cell lung cancer who are African American are 13 percent less likely to be treated with immunotherapy compared with those who are white (329).

other clinical trials, adding prostate-targeted radiotherapy to standard treatment for metastatic prostate cancer significantly increased survival for patients who had limited metastatic disease (344) (345). These data, together with the data on using surgery to treat oligometastatic disease (see **Using Surgery to Treat Metastatic Cancer,** p. 73), highlight how research is improving outcomes for patients with limited metastatic disease.

Despite the immense benefits of radiotherapy, it can have long-term adverse effects that negatively impact patient quality of life. Intensity-modulated radiotherapy (IMRT) is an advanced approach to radiotherapy in which specialized imaging, usually computed tomography (CT) or MRI, and planning software are used to deliver high-energy beams of radiation. There are multiple beams of radiation divided into many "beamlets," each of which can have a different intensity. Given that IMRT delivers radiation in a way that more precisely fits the shape and size of the tumor compared with conventional radiotherapy, healthy tissues surrounding a tumor are spared from damage caused by the radiation, which can reduce the adverse effects of radiotherapy. This benefit of using an advanced approach to radiotherapy was highlighted recently by the demonstration that patients with cervical or endometrial cancer who received IMRT after surgery rather than conventional radiotherapy reported a reduction in adverse events from the treatment, including a reduction in adverse gastrointestinal events such as diarrhea and fecal incontinence (346).

Treatment with Cytotoxic Chemotherapy

Cytotoxic chemotherapy was the third type of treatment to become a pillar of cancer care (see **Figure 14,** p. 75). It remains the backbone of treatment for many patients with cancer to this day, although its use is constantly evolving as researchers develop new cytotoxic chemotherapeutics and identify new ways to use existing cytotoxic chemotherapeutics to improve survival and quality of life for patients.

Increasing Options for Patients with Small Cell Lung Cancer

In June 2020, the FDA approved a new cytotoxic chemotherapeutic called lurbinectedin (Zepzelca) for treating adults who have small cell lung cancer (SCLC) that has progressed despite treatment with a platinum-based cytotoxic chemotherapeutic such as cisplatin or carboplatin.

SCLC accounts for about 13 percent of the lung cancer cases diagnosed each year in the United States (5). This translates to almost 30,000 cases of the disease in 2020. Most patients are diagnosed with metastatic disease. Even with treatment, which is commonly a combination of carboplatin or cisplatin and

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, it is necessary to perform surgery to obtain a tumor sample, or biopsy, for diagnosing cancer.

Surgery to Debulk a Cancer: In some cases, such as if a tumor is extremely large and/or located very close to important organs or tissues, only part of the tumor is removed.

Surgery to Stage Cancer: In some cases, it is necessary to perform surgery to determine how far a cancer has spread from the site at which it arose. This information is vital for establishing the best treatment plan for a patient.

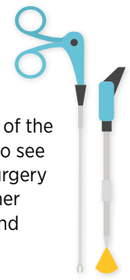
Surgery to Ease Problems Caused by a Cancer: In some cases, most commonly for patients with advanced cancer, surgery can be performed palliatively to remove tumors that are causing pain, pressure, or blockages.

Surgery to cure cancer: In some cases, most commonly when cancer is confined to one area of the body, surgery can be performed with curative intent. During such a surgery, the entire tumor is removed.

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.



the cytotoxic chemotherapeutic etoposide, most patients have disease progression. In this situation, the only FDA-approved therapeutic is the cytotoxic chemotherapeutic topotecan, but it leads to tumor responses in only about 16 percent of patients and median survival is less than 8 months (347).

The approval of lurbinectedin was based on results from a phase II clinical trial that showed that 35 percent of patients had partial tumor shrinkage (347). These responses lasted for a median of 5.3 months. Further follow-up of the patients is required to determine whether lurbinectedin will improve overall survival for patients with metastatic SCLC, but the accelerated approval of the cytotoxic chemotherapeutic provides new hope for patients with this deadly disease.

Using Cytotoxic Chemotherapy to Reduce the Need for Surgery

In April 2020, the FDA approved a novel formulation of the cytotoxic chemotherapeutic mitomycin for treating patients with low-grade upper tract urothelial cancer. The new mitomycin formulation is called Jelmyto.

Urothelial cancer arises in cells called urothelial cells. These cells line the urethra, bladder, ureters, renal pelvis, and some other organs. Most urothelial cancers occur in the bladder, but some occur in the ureters, which are the tubes that connect the kidneys to the bladder, and the renal pelvis, which is the very top part of the ureters. These cancers are collectively referred to as upper tract urothelial cancers.

USING RADIATION IN CANCER CARE

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

Radiotherapy

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

Radiology

Radiology largely uses lower-energy radiation to image tissues to diagnose disease or treat disease via the minimally invasive techniques used in interventional radiology.

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 chiefly by damaging DNA, leading to cancer cell death with relative sparing of normal tissues.

Uses of Radiotherapy

- **Curative Radiotherapy** seeks to eliminate cancers, particularly small cancers and locally advanced cancers; it is often used in combination with systemic therapy.
- **Adjuvant Radiotherapy** seeks to eliminate any remaining cancer following prior treatment.
- **Neoadjuvant Radiotherapy** is used to shrink a cancer so that it can be subsequently treated by a different method such as surgery.
- **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, typically 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 multiple directions. Imaging of the treatment area is typically performed using low-energy diagnostic X-rays. It is chiefly 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 fit the shape and size of the tumor.
  - Intensity-modulated radiotherapy (IMRT) is a further 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. IMRT is particularly useful when a sharp dose gradient is required between the tumor and sensitive tissues, for example, the optic nerves.
  - 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 many (typically more than eight) beams with a highly sophisticated imaging system to direct radiation to very well-defined smaller tumors. Typically, 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 pass though the body, losing energy and causing 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-177 dotatate (Lutathera) to treat gastroenteropancreatic neuroendocrine tumors.

Adapted from (40)

One of the main factors affecting outcomes for patients with upper tract urothelial cancer is the grade of the tumor. Low-grade upper tract urothelial cancer is usually not invasive and does not spread outside the ureter or kidney. It is a rare type of cancer; there are only 6,000 to 8,000 new patients diagnosed with the disease each year in the United States.

Most patients who have low-grade upper tract urothelial cancer are treated through surgery. In many cases, the surgery has to be very extensive, involving the complete removal of the affected kidney, ureter, and bladder cuff.

The cytotoxic chemotherapy gel provides a new, minimally invasive approach to treating low-grade upper tract urothelial cancer. The mitomycin is delivered to the cancer in a reverse thermal hydrogel that is given to patients using a ureteral catheter or nephrostomy tube. The cytotoxic chemotherapy gel is chilled at the time of administration and slowly becomes liquid as it warms up over the course of several hours before being excreted in the urine. Its approval was based on results from a phase III clinical trial that showed that 58 percent of patients had complete tumor shrinkage following six treatments of the gel administered weekly. Among these patients, 46 percent continued to have complete tumor shrinkage after 12 months, 22 percent had not yet been followed for 12 months, and the rest had disease recurrence.

Mitomycin has been previously approved by the FDA in alterative formulations for treating certain patients with either stomach cancer or pancreatic cancer. By developing a new formulation of the cytotoxic chemotherapeutic, researchers are building on prior knowledge generated in the cycle of medical research to drive progress for patients with cancer.

Treatment with Molecularly Targeted Therapy

Extraordinary advances in our understanding of the biology of cancer, including the identification of numerous genetic mutations that fuel tumor growth in certain patients, set the stage for the new era of precision medicine. In this era, the standard of care for many patients is changing from a one-size-fits-all approach to one in which greater understanding of the individual patient and the characteristics of his or her cancer dictates the best treatment option for the patient (see **Understanding How Cancer Develops,** p. 19).

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 these molecularly targeted therapeutics tends to make them more effective and less toxic than cytotoxic chemotherapeutics. As a result, they are not only saving the lives of patients with cancer, but also allowing these individuals to have a higher quality of life than many who came before them.

In the 12 months spanning August 1, 2019 to July 31, 2020, the FDA approved 16 new molecularly targeted anticancer therapeutics (see **Table 6,** p. 74). During this period, they also approved nine previously approved molecularly targeted anticancer therapeutics for treating additional types of cancer. For example, in April 2020, the FDA approved the molecularly targeted therapeutic encorafenib (Braftovi) for use in combination with another molecularly targeted therapeutic called cetuximab (Erbitux) for treating adults who have metastatic colorectal cancer fueled by a BRAF V600E mutation that has progressed despite prior treatments. This approval followed the original approval of encorafenib for treating melanoma, which was highlighted in the *AACR Cancer Progress Report 2018* (212).

Targeting an Array of Cancers That Share the Same Genetic Alteration

One of the most significant precision medicine advances in the 12 months spanning this report was the FDA approval of a second molecularly targeted therapeutic to treat cancer based on the presence of a specific genetic biomarker in the tumor irrespective of the site at which the tumor originated. The therapeutic, entrectinib (Rozlytrek), was approved by the FDA in August 2019 for treating children and adults who have solid tumors that test positive for the NTRK gene fusion biomarker and who have no other options for treatment.

Entrectinib targets three related proteins called TRKA, TRKB, and TRKC. The genes NTRK1, NTRK2, and NTRK3 provide the code that cells use to make these proteins. Entrectinib also targets two other proteins, ROS1 and ALK.

Research has shown that genetic alterations known as chromosomal translocations that involve the three NTRK genes and lead to the production of TRK fusion proteins drive the growth of up to 1 percent of all solid tumors (348). These solid tumors encompass a wide array of cancer types that occur in adults and children, including many rare cancers, such as mammary analogue secretory carcinoma of the salivary gland, infantile fibrosarcoma, and cholangiocarcinoma.

Entrectinib was approved based on combined data from several phase I and phase II basket trials (349) (see **Figure 13,** p. 72). The data showed that 57 percent of patients treated with the molecularly targeted therapeutic had complete or partial tumor shrinkage. Tumor shrinkage was seen across a range of cancer types, including NSCLC, mammary analogue secretory carcinoma of the salivary gland, breast cancer, colorectal cancer, thyroid cancer, pancreatic cancer, and sarcomas. Recent promising results from another clinical trial showed that entrectinib could also benefit children with brain and other solid tumors harboring alterations in NTRK1/2/3, ROS1, or ALK genes (349a) including in pediatric glioma, a type of brain cancer that **Camden Green** was diagnosed with in 2018 (see p. 80).

CAMDEN GREEN
AGE 6 | ASHEVILLE, NORTH CAROLINA

Fighting Childhood Cancer with Entrectinib

A message from Steve and Kathrine Green, Cami's parents.

In June 2018, we were told that our four-year-old daughter Cami had a brain tumor and that she had just three to six months to live. We were devastated but refused to give up hope. Testing of the tumor for genetic alterations matched Cami with an oral treatment called entrectinib (Rozlytrek) that was being tested in a clinical trial. We enrolled Cami in the trial, and the results have been amazing. There is no evidence of cancer by MRI, and other than some minor side effects, Cami is healthy and happy.

Our world was turned upside down over the course of a few weeks in the summer of 2018. Cami was an energetic child who loved singing and dancing. Then, one evening, she felt unwell going to bed and spent the night throwing up. We weren't too concerned but when we checked on her around 5 a.m. the next morning, she was blue and unresponsive.

We immediately called 911. As Steve was holding Cami while we waited for the ambulance, her body stiffened, and she seemed to be having a seizure.

Steve rode with Cami in the ambulance to the local hospital. They were rushed to the emergency room where 15 to 20 health care professionals were waiting for Cami. The hospital chaplain came over after a minute or two, and we feared the worst.

Fortunately, the doctors were able to stabilize Cami and we breathed a massive sigh of relief, but it was just the beginning of our journey.

The last in a series of tests and scans at the local hospital was an MRI. The news was bad; there were three to five areas of concern in Cami's brain, and even though multiple radiologists had looked at the MRI, the doctors did not know what was wrong.

We took Cami to the University of North Carolina at Chapel Hill to find answers. Finally, after two weeks, during which we kept getting worse and worse news, we learned that Cami had a brain tumor called a high-grade glioma. We were told that she had three to six months to live. We were also told that whole-brain radiotherapy might add a year to Cami's life but that we should consider just going home and enjoying the time we had left with Cami rather than putting her through this harsh treatment.

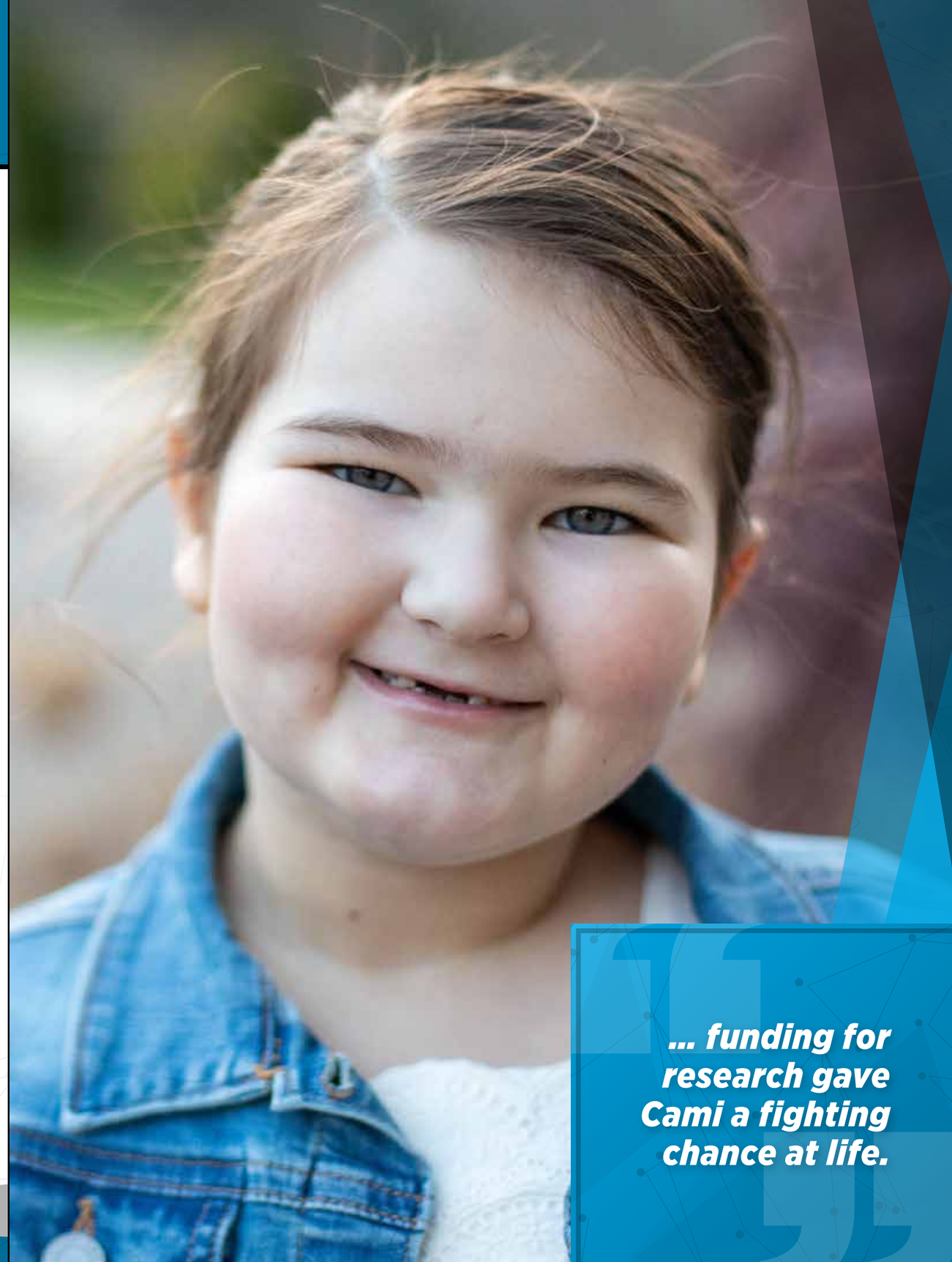
We didn't give up. We reached out to everyone we could think of and traveled to different children's hospitals seeking advice from the best minds in pediatric oncology. All this brainstorming led us to move forward along two paths. First, we followed a friend's advice and asked the doctors to send a sample of Cami's tumors for genetic profiling. Second, we considered a clinical trial that would involve brain surgery to debulk the tumors, followed by chemotherapy, then radiotherapy, and then a stem-cell therapy. The doctors told us this trial would give Cami a 10 percent chance of survival.

Just 72 hours before Cami was scheduled to have the debulking surgery, we got a call from a pediatric neuro-oncologist at St. Jude Children's Research Hospital. He had received results from the genetic profiling of the tumors, which showed that they had a genetic alteration called a ROS1 fusion. He told us that there was a clinical trial testing a treatment targeting tumors characterized by ROS1 fusions and that the treatment would consist of taking two pills a day for three years. The treatment plan seemed so simple that we immediately chose that clinical trial over the one that involved surgery.

Cami has been taking entrectinib for two years. Before she began the treatment, brain MRIs showed three obvious tumors and two other areas of concern. Within three months of starting entrectinib, the three tumors had disappeared. These tumors have not recurred, and the other two areas of concern have not changed at all, so the doctors aren't sure if they are tumors.

Cami experiences two main side effects as a result of taking entrectinib. She has gained weight and has problems with her bones, which fracture very easily. She doesn't feel pain when the fractures happen, so we even had a time when she was walking, jumping, and dancing with two broken femurs!

Despite the fractures, Cami is having fun and living life to the full. We could not be more grateful to all the researchers who played a part in developing entrectinib and all the health care professionals who played a part in caring for Cami. We want Congress to know that funding for research gave Cami a fighting chance at life, and every family deserves this chance.



... funding for research gave Cami a fighting chance at life.

COMPANION DIAGNOSTICS

The effective use of anticancer therapeutics targeting defined cancer-driving molecular abnormalities often requires tests called companion diagnostics. Companion diagnostics:

- are stringently tested for accuracy, sensitivity, and fidelity;

- are regulated by the U.S. Food and Drug Administration;

- accurately match patients with a specific therapy;

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

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

Adapted from (1)

Providing New Treatments for Patients with Lung Cancer

Lung cancer is the second most commonly diagnosed cancer in the United States, with about 228,820 new cases expected to be diagnosed in 2020 (5). About 84 percent of lung cancers diagnosed in the United States are classified as NSCLC.

In the past decade, researchers have significantly increased our understanding of the genetic changes that fuel NSCLC growth in certain patients and developed therapeutics that target some of these changes (350) (351). Despite the emergence of molecularly targeted therapy as a groundbreaking new treatment for patients with NSCLC, a recent international survey of physicians who treat such patients found that 61 percent of all respondents believe that fewer than 50 percent of patients with lung cancer in their country have their tumors tested for the genetic mutations that determine whether the patient is eligible for these treatments (352). Even among physicians in the United States and Canada, 51 percent thought this was the case. The results of this survey highlight the need for efforts to increase awareness and use of molecular testing of patients with lung cancer around the world.

About one percent of NSCLC cases are fueled by chromosomal translocations that involve the ROS1 gene and lead to the production of ROS1 fusion proteins (353). The ROS1-targeted therapeutic entrectinib was approved by the FDA in August 2019 as an initial treatment for patients with metastatic NSCLC that tests positive for chromosomal translocations involving the ROS1 gene. The approval was based on results from three phase I and phase II basket trials that showed that 78 percent of patients who received entrectinib had partial or complete tumor shrinkage (354).

Another 3 to 4 percent of NSCLCs are fueled by mutations in the MET gene that result in the part of the gene called exon 14 being missing (355). In May 2020, the FDA approved the first MET-targeted therapeutic, capmatinib (Tabrecta). It was approved for treating patients with metastatic NSCLC that tests positive for MET exon 14 skipping mutations using a specific companion diagnostic called FoundationOne CDx (see sidebar on **Companion Diagnostics,** p. 82). The approval was based on results from a phase II clinical trial that showed that 68 percent of patients who received capmatinib as their initial treatment had partial or complete tumor shrinkage. Among patients who received capmatinib after other treatments, 41 percent had partial or complete tumor shrinkage.

Yet another 1 to 2 percent of NSCLCs are fueled by chromosomal translocations that involve the RET gene and lead to the production of RET fusion proteins (356). In May 2020, the FDA approved the first RET-targeted therapeutic, selpercatinib (Retevmo), for treating patients with metastatic NSCLC that tests positive for chromosomal translocations involving the RET gene. The approval was based on results from a phase I/II clinical trial that showed that 85 percent of patients who received selpercatinib as their initial treatment had partial or complete tumor shrinkage. Among patients whose NSCLC had progressed after platinum-based chemotherapy, 64 percent had partial or complete tumor shrinkage.

In May 2020, selpercatinib was also approved by the FDA for treating certain patients with thyroid cancer. It is projected that 52,890 new cases of the disease will be diagnosed in 2020 (5). Papillary thyroid cancer is the most common type of thyroid cancer. Chromosomal translocations involving the RET gene are found in up to 20 percent of these cancers (356). For medullary thyroid cancer, more than 50 percent of cases are fueled by other types of RET gene mutation (see sidebar on **Genetic Mutations,** p. 22). The FDA approved selpercatinib specifically for patients age 12 or older who have advanced or metastatic medullary thyroid cancer that tests positive for RET gene alterations and who require systemic therapy, and for patients age 12 and older who have advanced or metastatic thyroid cancer that tests positive for chromosomal translocations involving the RET gene, who require systemic therapy, and whose cancer is not responding to standard treatment with radioactive iodine. These two approvals were based on results from the same clinical trial that led to the approval of selpercatinib for NSCLC. Among patients with medullary thyroid cancer that tests positive for RET gene alterations, 73 percent had partial or complete tumor shrinkage. Among those with thyroid cancer that tests positive for chromosomal translocations involving the RET gene and that is not responding to radioactive iodine, 100 percent had partial or complete tumor shrinkage.

Expanding the Uses for PARP-targeted Therapeutics

The number of cancer types for which therapeutics targeting poly ADP-ribose polymerase (PARP) proteins are an FDA approved treatment doubled in the 12 months covered by this report. On August 1, 2019, there was at least one PARP-targeted therapeutic approved to treat certain patients with breast cancer or ovarian cancer. As of July 31, 2020, certain patients with pancreatic cancer or with prostate cancer were also eligible for treatment with these molecularly targeted therapeutics (see **Table 6,** p. 74).

The development and FDA approval of PARP-targeted therapeutics was based on decades of basic and clinical research (358). PARP proteins have a key role in one of the many pathways that cells use to repair damaged DNA, the base excision repair pathway (359). Blocking this pathway with PARP-targeted therapeutics reduces the ability of a cell to repair damaged DNA.

Deficiencies in other DNA repair pathways are found in some cancers. In some patients, these deficiencies are inherited. For example, inherited mutations in homologous recombination modifying genes such as BRCA1 and BRCA2 are associated with hereditary breast and ovarian cancer syndrome (see **Table 2,** p. 23). However, mutations in these and other DNA repair pathway genes can also arise during a patient's lifetime and are found in sporadic tumors.

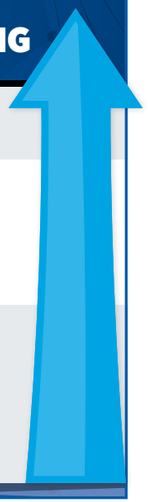
THYROID CANCER INCIDENCE IS RISING

Worldwide the number of thyroid cancer cases increased from about

95,000
IN 1990

to more than

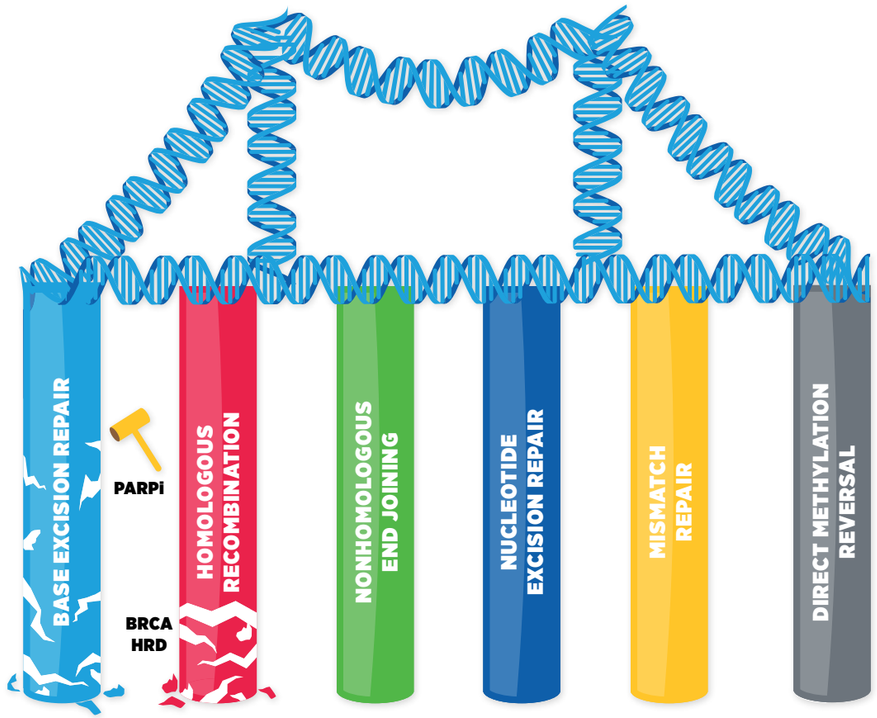
255,000
IN 2017
(357).



Although PARP and BRCA proteins work in different DNA repair pathways, disruption to both pathways can ultimately trigger cell death (see **Figure 15,** p. 83). Therefore, cancer cells harboring cancer-associated BRCA1 or BRCA2 (BRCA1/2) mutations that disable the BRCA proteins to repair damaged DNA are particularly susceptible to PARP-targeted therapeutics (359). As a result of these discoveries, PARP-targeted therapeutics were first developed and approved for treating women with advanced ovarian cancer who have inherited a cancer-associated BRCA1/2 mutation.

As researchers learned more about the biology of cancer, it was determined that mutations in genes other than BRCA1/2 can disrupt the homologous recombination DNA repair pathway (359). Homologous recombination deficiency (HRD) leads to the accumulation of DNA damage, a situation known as genomic instability, which, in turn, can lead to cancer. Therefore, researchers tested whether HRD might provide a new biomarker for cancers susceptible to PARP-targeted therapeutics. In October 2019, the FDA approved the PARP-targeted therapeutic niraparib (Zejula) for treating women with ovarian cancer, fallopian tube cancer, or primary peritoneal cancer that has progressed despite treatment with at least three different cytotoxic chemotherapy regimens and that tests positive for HRD using the myChoice CDx companion diagnostic. The myChoice CDx companion diagnostic determines HRD status by testing for the presence of cancer-associated BRCA1/2 mutations and three other markers of genomic instability. The approval was based on results from a phase II clinical trial that showed that 24 percent of patients who had HRD-positive advanced ovarian cancer had partial tumor shrinkage.

FIGURE 15 DNA INTEGRITY: BRIDGING THE PRECISION GAP



Basic research has shown that maintenance of DNA integrity is essential for a cell to remain healthy and maintain normal function. The integrity of DNA is constantly under threat from errors that occur during multiplication, as well as exposure to chemicals, such as those in cigarette smoke, and ultraviolet radiation from the sun. If DNA is not appropriately repaired, mutations accumulate, increasing the chance that a cell will become cancerous. As a result, cells have several interrelated pathways that they use to repair damaged DNA (360). Individuals with genetic mutations that result in deficiency in the homologous recombination DNA repair pathway (HRD), including mutations in the BRCA1 and BRCA2 genes, have an increased risk of developing certain types of cancer. The PARP proteins are central to the base excision repair pathway (light blue support). Researchers have found that breast, ovarian, pancreatic, and prostate cancers with genetic mutations that lead to homologous recombination deficiency are responsive to PARP-targeted therapeutics because disruption of two DNA repair pathways leads to such pervasive DNA damage that the cancer cells die.

Adapted from (40)

The success of the PARP-targeted therapeutics as treatments for breast and ovarian cancer fueled by an inherited BRCA1/2 mutation led researchers to investigate whether these molecularly targeted therapeutics might also benefit patients with other types of cancer fueled by mutations in BRCA1/2 and other genes that cause HRD.

Pancreatic cancer is one of the deadliest types of cancer; just 9 percent of patients are alive five years after diagnosis (5). Researchers estimate that 4 to 7 percent of pancreatic cancers diagnosed in the United States are attributable to an inherited BRCA1/2 mutation (361). In December 2019, the FDA approved the PARP-targeted therapeutic olaparib (Lynparza) for treating patients with metastatic pancreatic cancer that has not progressed during first-line treatment with a platinum-based chemotherapy regimen and who have an inherited BRCA1/2 mutation, as determined using the BRACAnalysis CDx companion diagnostic. The approval was based on results from a phase III clinical trial that showed that treatment with olaparib almost doubled the median time to disease progression (361). Progression-free survival was 7.4 months for those who received olaparib compared with 3.8 months for those who received placebo.

Prostate cancer is the most commonly diagnosed cancer among men living in the United States (5). In 2020 alone, more than 191,000 men are expected to be newly diagnosed with the disease. Research has shown that up to 30 percent of prostate cancers have mutations in genes that influence the homologous recombination DNA repair pathway, most commonly BRCA1/2 or ATM (362). In May 2020, the FDA approved two PARP-targeted therapeutics for treating certain groups of men with metastatic prostate cancer fueled by mutations in genes that influence the homologous recombination DNA repair pathway, olaparib and rucaparib (Rubraca).

Initially, men who are diagnosed with metastatic prostate cancer are often treated with therapeutics that target androgens, the hormones that fuel prostate cancer growth. When the cancer stops responding to these treatments, it is referred to as castration-resistant prostate cancer. Olaparib was approved for treating men who have metastatic castration-resistant prostate cancer that has progressed despite treatment with enzalutamide (Xtandi) or abiraterone (Zytiga) and that has a mutation in any gene that influences the homologous recombination DNA repair pathway, including BRCA1/2. The FoundationOne CDx companion diagnostic can be used to identify any mutation causing homologous recombination DNA repair pathway deficiency, including BRCA1/2 mutations, and the BRACAnalysis CDx companion diagnostic can be used to detect BRCA1/2 mutations. The approval was based on results from a phase III clinical trial that showed that treatment with olaparib improved overall survival compared with treatment with either enzalutamide or abiraterone (362).

Rucaparib was approved for a slightly different group of men who have metastatic castration-resistant prostate cancer, those whose cancer has progressed despite treatment with an androgen receptor–directed therapy and a taxane-based cytotoxic chemotherapeutic such as docetaxel and has a cancer-associated BRCA1/2 mutation. The approval was based on results from a phase II clinical trial that showed that 44 percent of patients who received rucaparib had partial or complete tumor shrinkage.

Increasing Options for Treating Breast Cancer

Breast cancer is the most commonly diagnosed cancer among women living in the United States (5). In 2020 alone, 276,480 women and 2,620 men are expected to be newly diagnosed with the disease. Even though remarkable progress is being made against the disease, as illustrated by the fact that the overall breast cancer death rate decreased by 40 percent from 1989 to 2017 (363), breast cancer remains the second-leading cause of cancer-related death for women in the United States (5).

For patients with breast cancer, one factor determining what treatment options should be considered is the presence or absence of three tumor biomarkers, two hormone receptors and HER2. About 15 percent of breast cancers diagnosed the United States are characterized as HER2-positive (363). HER2-positive breast cancer tends to be aggressive, and the outcome for patients was typically poor until research led to the development and FDA approval of HER2-targeted therapeutics. Trastuzumab (Herceptin) was the first of these groundbreaking therapeutics to be approved by the FDA, in 1998.

There are now numerous HER2-targeted therapeutics approved for treating advanced or metastatic HER2-positive breast cancer. Most patients are first treated with a combination of trastuzumab, a second HER2-targeted therapeutic called pertuzumab (Perjeta), and a cytotoxic chemotherapeutic. These therapeutics were always given intravenously until July 2020, when a combination of trastuzumab, pertuzumab, and hyaluronidase–zzxf called Phesgo that can be given subcutaneously (under the skin) was approved by the FDA as an alternative option. Despite the success of the trastuzumab–pertuzumab combination, most HER2-positive breast cancers eventually progress because they become treatment resistant (see sidebar on **The Challenge of Treatment Resistance,** p. 86). Recent FDA decisions have provided two new molecularly targeted therapeutics, fam-trastuzumab deruxtecan-nxki (Enhertu) and tucatinib (Tukysa), to help address this challenge.

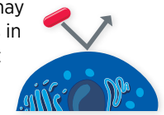
Fam-trastuzumab deruxtecan-nxki is a type of molecularly targeted therapeutic called an antibody-drug conjugate. It comprises a cytotoxic agent, deruxtecan, attached to the HER2-targeted antibody trastuzumab by a linker. When the antibody attaches to HER2 on the surface of breast cancer cells, the antibody-drug conjugate is internalized by the cells. This leads to deruxtecan being released from the linker and antibody. Once free, the deruxtecan is toxic to the breast cancer cells, which ultimately die.

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.

Adapted from (1)

Fam-trastuzumab deruxtecan-nxki was approved by the FDA in December 2019 for treating adults with metastatic HER2-positive breast cancer that has progressed despite treatment with two or more other HER2-targeted treatment regimens. The approval was based on results from a phase II clinical trial that showed that just over 60 percent of the patients who received the recommended dose of fam-trastuzumab deruxtecan-nxki had partial or complete tumor shrinkage (364).

Like all cancer treatments, fam-trastuzumab deruxtecan-nxki can have adverse effects, some of which can be very severe. One of the most concerning and, in some cases, life-threatening, is interstitial lung disease. Therefore, the FDA approved fam-trastuzumab deruxtecan-nxki with a boxed warning for interstitial lung disease and recommends that patients being treated with the molecularly targeted therapeutics be monitored for signs and symptoms of interstitial lung disease, including cough, dyspnea (difficult or labored breathing), fever and other new or worsening respiratory symptoms. If interstitial lung disease is suspected, further testing and intervention should be considered.

Tucatinib blocks HER2 from sending signals that promote the multiplication and survival of breast cancer cells. It was approved by the FDA in April 2020 for use in combination with trastuzumab and the cytotoxic chemotherapeutic capecitabine in the treatment of adults who have advanced or metastatic HER2-positive breast cancer that has progressed despite treatment with one or more other HER2-targeted therapeutics. The approval was based on results from a phase II clinical trial that showed that adding tucatinib to trastuzumab and capecitabine significantly improved median overall survival (365). Among patients who had metastases in the brain, which are particularly hard to treat, the median time to disease progression was significantly longer for those who received tucatinib.

About 10 percent of all breast cancers diagnosed in the United States test negative for HER2 and the two hormone receptors (363). This type of breast cancer, which is often referred to as triple-negative breast cancer, is highly aggressive. Patients often have poor outcomes, in part because cytotoxic chemotherapeutics were the only systemic treatment options for patients with metastatic triple-negative breast cancer until recently. Even with such treatments, the median overall survival is estimated to be less than 18 months (366).

In April 2020, the FDA approved an antibody-drug conjugate called sacituzumab govitecan-hziy (Trodelvy) for treating adults who have metastatic triple-negative breast cancer that has progressed despite the patient having tried at least two other treatment regimens. Sacituzumab govitecan-hziy comprises an antibody that targets the protein Trop-2, which researchers have detected in a high proportion of triple-negative breast cancers, attached by a linker to a cytotoxic agent called SN-38. When the antibody attaches to Trop-2 on the surface of triple-negative breast cancer cells, the antibody-drug conjugate is internalized by the cells. This leads to SN-38 being released from the linker and antibody. Once free, the SN-38 is toxic to the cancer cells, which ultimately die. Sacituzumab govitecan-hziy was approved by the FDA after it was shown in a phase I/II clinical trial to cause partial or complete tumor shrinkage for 33 percent

RECENT ADVANCES AGAINST BLOOD CANCERS

In the 12 months from August 1, 2019 to July 31, 2020, 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:

Chronic Lymphocytic Leukemia and Small Lymphocytic Lymphoma

- Acalabrutinib (Calquence) is a molecularly targeted therapeutic approved in November 2019.

Follicular Lymphoma

- Tazemetostat (Tazverik) is a molecularly targeted therapeutic approved in June 2020 (see **Using Epigenetic Therapy to Treat Cancer, p. 90**).

Multiple Myeloma

- Isatuximab-irfc (Sarclisa) is an immunotherapeutic approved in March 2020 for use in combination with pomalidomide (Pomalyst) and dexamethasone (see **Directing the Immune System to Cancer Cells, p. 109**).

Myelofibrosis

- Fedratinib (Inrebic) is a molecularly targeted therapeutic approved in August 2019.

Diffuse Large B-cell Lymphoma

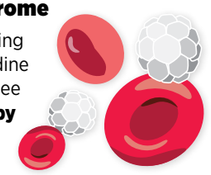
- Selinexor (Xpovio) is a molecularly targeted therapeutic approved in June 2020.
- Tafasitamab-cxix (Monjuvi) is an immunotherapeutic approved in July 2020 (see **Directing the Immune System to Cancer Cells, p. 109**).

Mantle Cell Lymphoma

- Brexucabtagene autoleucel (Tecartus) is an immunotherapeutic approved in July 2020 (see **Increasing the Cancer-killing Capacity of the Immune System, p. 108**).
- Zanubrutinib (Zankinsa) is a molecularly targeted therapeutic approved in November 2019.

Myelodysplastic Syndrome

- Inqovi is a tablet containing decitabine and cedazuridine approved in July 2020 (see **Using Epigenetic Therapy to Treat Cancer, p. 90**).



of patients who received the antibody-drug conjugate. Although more time is needed to determine there is also a survival benefit, sacituzumab govitecan-hziy has already transformed the lives of many patients with triple-negative breast cancer, such as **Ferda Martin** (see p. 88).

Adding Precision to Treatment for Blood Cancers

Cancers that arise in blood-forming tissues, such as the bone marrow, or in cells of the immune system are called blood cancers, or hematologic cancers. In the 12 months covered by this report, the FDA has made numerous decisions that are transforming the lives of patients with a wide array of hematologic cancers (see sidebar on **Recent Advances against Blood Cancers,** p. 87). Among these decisions are the approval of two new molecularly targeted therapeutics for use in the treatment of certain types of these diseases and the expansion of the uses of three previously approved molecularly targeted therapeutics to include the treatment of additional types of blood cancer.

Non-Hodgkin lymphoma is the most commonly diagnosed blood cancer in the United States. In 2020, 77,240 people in the United States are expected to be newly diagnosed with the disease and 19,940 to die from it (5).

The term non-Hodgkin lymphoma encompasses many different types of cancer, most of which arise in immune cells called B cells. Two molecularly targeted therapeutics to be recently approved by the FDA for treating different types of non-Hodgkin lymphoma arising in B cells—zanubrutinib (Zankinsa) and acalabrutinib (Calquence)—target a protein

FERDA MARTIN

AGE 52 | SAN FRANCISCO, CALIFORNIA

Looking Forward to the Future Despite Metastatic Breast Cancer

I was diagnosed with triple-negative breast cancer, which is a very aggressive disease, in March 2017. As a single mom, all I could think about was, "What will happen to my daughter?" She was just 7½ years old. In spring 2020, when I learned that the cancer had metastasized, it felt as if the light at the end of the tunnel was dimming, but treatment with sacituzumab govitecan-hziy (Trodelvy) shrank the tumor dramatically, and I feel so much more optimistic. I am looking forward to seeing my daughter finish middle school, graduate from high school, get her diploma in college, and start a career.

It all started in early 2017. I noticed that my left breast was incredibly sensitive, painful, and swollen. It was causing me so much discomfort that I had trouble sleeping at night on my left side. I made an appointment to see my doctor, but when I arrived, she was not available so I met with a nurse practitioner. I was told that I had fibrocystic breasts and not to worry. However, I was in so much pain that I insisted I get a referral for a mammogram.

Unfortunately, I had to wait 30 days for the mammogram. By the time I went for the procedure, the tumor was so large that a surgeon and doctor were called immediately so that they could perform a biopsy. Within days, I met with an oncologist at UCSF to come up with a treatment plan. After a medication I received through a clinical trial for a week or two did nothing to slow the growth of the tumor, I began chemotherapy with carboplatin and paclitaxel. My heart rate plummeted following my third infusion, and I was hospitalized for three days. The tumor was still growing so my oncologist switched me to a different chemotherapy regimen, cyclophosphamide and doxorubicin. This was the most grueling treatment I have received so far.

Once I had completed four cycles of cyclophosphamide and doxorubicin, I had a double mastectomy. During the surgery, they discovered that the cancer had spread to my lymph nodes; 17 of 25 lymph nodes that they removed tested positive for cancer. The official diagnosis was stage III triple-negative breast cancer; I was devastated, and began preparing for what would happen to my daughter if I were to die.

The surgery was followed by radiation and more chemotherapy, this time with capecitabine, to keep the cancer from recurring. Capecitabine was challenging. I couldn't walk more than three blocks without feeling like I was going to have a heart attack; I had heavy perspiration, and night sweats. But overall, I was glad to be alive.

After the capecitabine, I participated in several clinical trials, including one testing an immunotherapy called pembrolizumab (Keytruda) and one testing a therapeutic vaccine, to keep the cancer from recurring. At that time, the cancer was not detectable, and I was able to spend quality time with my daughter. We travelled to so many places—Paris, Istanbul, Lake Tahoe, Palm Springs, and Half Moon Bay. I am so grateful for the time that we have had together to make memories for her.

In March 2020, the therapeutic vaccine treatment that I had been scheduled to receive was cancelled because the researchers stopped the clinical trial as a result of the COVID-19 pandemic. About a month later, I felt a round lump near my collarbone. It was the size of a marble and hard as a rock. I immediately made an appointment to see my oncologist. PET scans showed that the cancer had metastasized to lymph nodes at three sites: my collarbone area, my left side, and my abdomen.

My oncologist recommended I start a treatment that had just been approved by the FDA, sacituzumab govitecan-hziy. After the first infusion at the end of June 2020, I could feel the lump near my collarbone getting smaller. After five infusions I could no longer feel it at all. I will be having a PET scan soon and am hopeful that the results will be good.

I don't have significant side effects from the sacituzumab govitecan-hziy. I have lost my hair, have dry eyes, and feel a little fatigue some days, but I'm grateful to be alive. Cancer brought me clarity, and I embrace joy and happiness. I continue to make more memories with my daughter, we visit the museums in San Francisco, read books, eat out, and spend time at my family's blueberry farm in Oregon.

My wish is that nobody ever goes through what I have gone through in my cancer journey; it has been really tough. That is why it is imperative that our government fund cancer research. Cancer research helps people stay alive.

I'm grateful to be alive. Cancer brought me clarity, and I embrace joy and happiness.

called BTK, which is one component of a signaling pathway that promotes the survival and expansion of non-Hodgkin lymphoma B cells.

Zanubrutinib is a new BTK-targeted therapeutic that was approved by the FDA in November 2019 for treating certain adults who have an aggressive type of non-Hodgkin lymphoma called mantle cell lymphoma. Zanubrutinib was approved for treating those patients whose mantle cell lymphoma has progressed despite at least one prior treatment. The approval was based on combined results from a phase I/II clinical trial and a phase II clinical trial. In both trials, 84 percent of the patients had partial or complete tumor shrinkage following treatment with zanubrutinib.

Acalabrutinib was approved for treating patients with mantle cell lymphoma in October 2017 (212). In November 2019, the FDA added an approval for using the BTK-targeted therapeutic for treating adults who have chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL), which are slow-growing types of non-Hodgkin lymphoma. CLL and SLL are essentially the same disease but have different names depending on where in the body the non-Hodgkin lymphoma cells accumulate. CLL cells are found mostly in the blood and bone marrow, whereas SLL cells are found mostly in the lymph nodes. The CLL and SLL acalabrutinib approval was based on results from two phase III clinical trials that showed that the time before disease progressed was significantly longer among patients who received acalabrutinib compared with patients who received alternative standard treatments (367).

The most common type of non-Hodgkin lymphoma diagnosed in the United States is diffuse large B-cell lymphoma. There are several forms of this aggressive type of non-Hodgkin lymphoma but the most common is called diffuse large B-cell lymphoma, not otherwise specified. In June 2020, the FDA approved the molecularly targeted therapeutic selinexor (Xpovio) for treating patients with diffuse large B-cell lymphoma, not otherwise specified, whose disease has relapsed after or never responded to treatment with at least two other systemic treatments. Selinexor targets a protein called XPO1, which is found at elevated levels in diffuse large B-cell lymphoma cells. XPO1 helps move proteins out of a part of the cell called the nucleus. It is particularly linked to moving proteins that suppress tumor growth out of the nucleus. When selinexor targets XPO1, it forces these proteins to be retained in the nucleus where they can act to suppress tumor growth. The approval of selinexor was based on results from a phase II clinical trial that showed that 29 percent of patients had complete or partial tumor shrinkage after treatment with the new molecularly targeted therapeutic (368).

Myelofibrosis is a rare type of blood cancer. It is estimated that there are about 20,000 people living with the disease in the United States (369). In many cases, myelofibrosis is driven by mutations in the JAK2 gene. In August 2019, the FDA approved a new JAK2-targeted therapeutic, fedratinib (Inrebic), for treating certain patients who have myelofibrosis.

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

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

The likely outcome for patients diagnosed with myelofibrosis is estimated based on several risk factors. Patients with more than one risk factor — including being age 65 or older; having anemia; experiencing fever, night sweats, or weight loss; having high white blood cell counts; and having at least 1 percent of cells in the blood being cancer cells — are classed as having intermediate-2 risk disease. Patients with four or more risk factors are classed as high risk.

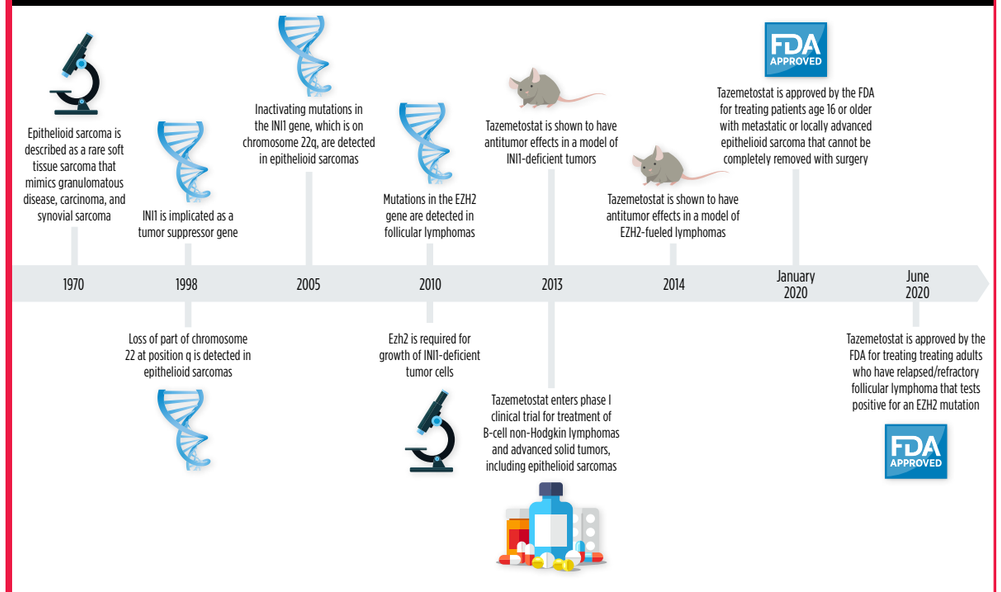
Fedratinib was approved for treating adults with intermediate-2 or high-risk primary or secondary myelofibrosis. The approval was based on results from a phase III clinical trial that showed that treatment with fedratinib significantly reduced spleen volume and reduced myelofibrosis-related symptoms compared with placebo (369).

Using Epigenetic Therapy to Treat Cancer

Research has shown that how and when genes are turned "on" or "off" is regulated by special factors called epigenetic modifications (see **Cancer Development: Influences inside the Cell,** p. 19). These modifications tag DNA or attach to histones. The sum of these modifications across the entire genome is called the epigenome.

Genetic mutations that disrupt the epigenome can lead to cancer development. For example, mutations that lead to loss of the protein INI1, which is involved in epigenetic regulation of gene accessibility, drive more than 90 percent of a rare type of cancer called epithelioid sarcoma (370). Researchers found that the multiplication and survival of cancer cells lacking INI1 protein depend on a protein called EZH2, which adds epigenetic modifications called methyl groups to histones (371).

FIGURE 16 RESEARCH MILESTONES ON THE ROAD TO DEVELOPING TAZEMETOSTAT



In January 2020, tazemetostat (Tazverik) became the first epigenetic therapy to be approved by the U.S. Food and Drug Administration (FDA) for treating a solid tumor, epithelioid sarcoma. It was specifically approved for treating patients age 16 or older with metastatic or locally advanced epithelioid sarcoma that cannot be completely removed with surgery. It was subsequently approved for treating certain patients with an aggressive type of non-Hodgkin lymphoma called follicular lymphoma. The initial description of epithelioid sarcoma as a distinct type of cancer in 1970 (370) was followed by decades of basic, translational, and clinical research, before the approval of tazemetostat as a treatment for the disease. One of the first research milestones on the way to the FDA approval was the discovery that damage to chromosome 22 at position q is characteristic of epithelioid sarcomas (372). This was followed by the demonstration that INI1, which is found at chromosome 22q, is a tumor suppressor gene (373), the identification of inactivating mutations in the INI1 gene in epithelioid cancers (374), and the discovery that INI1-deficient tumors cells are dependent on EZH2 for their growth (375). Other research showed that mutations in EZH2 frequently occur in follicular lymphoma and other types of B-cell non-Hodgkin lymphoma (376) and that targeting EZH2 has antitumor effects in preclinical models of lymphoma and solid tumors fueled by EZH2 mutations and INI1 mutations, respectively (377) (378). Together, this body of research led to the development of tazemetostat, which targets EZH2, and its testing in clinical trials as a treatment for B-cell non-Hodgkin lymphomas and advanced solid tumors, including epithelioid sarcomas.

Adapted from (40)

Tazemetostat (Tazverick) targets EZH2, preventing it from adding methyl groups to histones. It was approved by the FDA in January 2020, after several decades of basic, translational, and clinical research, for treating patients age 16 or older with metastatic or locally advanced epithelioid sarcoma that cannot be completely removed with surgery (see **Figure 16,** p. 91).

Epithelioid sarcoma is a type of soft-tissue sarcoma that usually arises in the soft tissue under the skin of a finger, hand, forearm, lower leg, or foot. In 2020, it is estimated that there will be 13,130 new cases of soft tissue sarcoma diagnosed in the United States in 2020 (5). Given that epithelioid sarcoma accounts for about 1 percent of soft

tissue sarcomas (379), it is projected that about 1,300 people will be diagnosed with the disease in 2020.

Tazemetostat was approved for treating metastatic or locally advanced epithelioid sarcoma after it was shown in a phase II clinical trial to cause partial or complete tumor shrinkage for 15 percent of patients who received the molecularly targeted therapeutic (370). The approval made tazemetostat the first therapeutic approved by the FDA specifically for treating patients with epithelioid sarcoma, like **Sandra Griego** (see p. 94), and the first epigenetic therapy for treating patients with a solid tumor.

In June 2020, the FDA approved tazemetostat for treating certain patients with a different type of cancer, follicular lymphoma. Follicular lymphoma is an aggressive type of non-Hodgkin lymphoma that arises in B cells. Up to 25 percent of these cancers are fueled by mutations in EZH2 (380). Tazemetostat was approved for treating adults who have follicular lymphoma that has relapsed after or never responded to treatment with at least two other systemic treatments and that tests positive for an EZH2 mutation using the cobas EZH2 Mutation Test companion diagnostic. This approval was based on results from a phase II clinical trial that showed that 69 percent of patients with EZH2 mutation–positive follicular lymphoma had complete or partial tumor shrinkage after treatment with tazemetostat. Tazemetostat was also approved for treating adults who have follicular lymphoma without an EZH2 mutation so long as the lymphoma has relapsed after or never responded to other treatments and there are no satisfactory alternative treatment options after it was shown in the phase II clinical trial that 34 percent of patients in this medical situation had complete or partial tumor shrinkage.

Research has shown that the addition of methyl groups to DNA is particularly important for promoting the growth of many types of blood cancer, including a group of rare blood cancers called MDS (381). This knowledge was harnessed in the development of the chemotherapeutic decitabine as a treatment for MDS in the mid 2000's (381). Decitabine disrupts the addition of methyl groups to DNA by proteins called DNA methyltransferases because it becomes incorporated into the DNA strands of MDS cells as they multiply and traps DNA methyltransferases in place, preventing them from adding further methyl groups to DNA.

Decitabine is given intravenously, which means that patients must travel to a health care facility to receive treatment. In July 2020, the FDA approved a tablet that contains decitabine together with another drug called cedazuridine, which prevents rapid breakdown of decitabine in the gut and liver, for treating certain patients with MDS. The new treatment, which is called Inqovi, has the potential to reduce the number of visits a patient must make to a health care facility, which is particularly important to patients during the COVID-19 pandemic.

MDS arises when the development of blood cells in the bone marrow goes awry. The type of MDS a person has, and therefore the symptoms he or she has, are determined by the type of blood cell affected and how it is affected. One of the most common systems for classifying MDS is the French-American-British system, which describes five main types of the disease: refractory anemia; refractory anemia with sideroblasts; refractory anemia with excess blasts; refractory anemia with excess blasts in transformation; and chronic myelomonocytic leukemia. The severity of a patient's disease, which is an important factor in deciding the individual's best treatment option, is determined using the International Prognostic Scoring System.

Inqovi was approved for treating adults who have refractory anemia, refractory anemia with sideroblasts, refractory anemia with excess blasts, or chronic myelomonocytic leukemia that is determined to be intermediate-1, intermediate-2, or high-risk using the International Prognostic Scoring System. The approval was based on cumulative data from two clinical trials that showed that about 20 percent of patients had a complete response following treatment with Inqovi (382) (383).

Bringing the Promise of Precision Medicine to Patients with Rare Cancers

A cancer type is defined as rare by the NCI if fewer than 40,000 people are newly diagnosed with the disease in a given year (384). Together, rare cancers account for about 27 percent of cancer cases and about 25 percent of cancer deaths each year in the United States.

Rare cancers can be challenging for researchers to study and for physicians to treat (see sidebar on **The Challenges Posed by Rare Cancers,** p. 93). However, during the 12 months covered by this report, August 1, 2019, to July 31, 2020, the FDA approved new molecularly targeted therapeutics for treating several types of rare cancer, bringing the promise of precision medicine to patients who often have few treatment options.

Gastrointestinal stromal tumors (GISTs) are soft tissue sarcomas that arise anywhere along the gastrointestinal tract but most commonly in the stomach or small intestine. It is estimated that there are around 3,300 to 6,000 new cases of GIST each year in the United States (388). The discovery that most GISTs are fueled by mutations in either the KIT gene or the PDGFRA gene led to the development and FDA approval of therapeutics that target KIT and PDGFRα. Imatinib (Gleevec) became the first of these molecularly targeted therapeutics approved by the FDA for treating GISTs in 2002.

Despite the success of imatinib as a treatment for patients with GIST that is metastatic, recurrent, or unresectable (meaning that it cannot be surgically removed), some tumors

THE CHALLENGES POSED BY RARE CANCERS

The National Cancer Institute (NCI) defines a type of cancer as rare if fewer than 40,000 people are diagnosed with the disease each year (384). All childhood cancers are considered rare cancers. Rare cancers pose significant challenges to many stakeholders in the cancer community, including patients, physicians, and researchers. According to the NCI, these challenges include:

Patients may find that it:

- takes a long time from when they first notice a symptom to the time when doctors know that the symptom is caused by a rare cancer and what type of cancer it is.
- is hard to find a physician who knows a lot about the rare cancer with which they have been diagnosed and how to treat it.
- is necessary to travel far to get treatment for a rare cancer.

Physicians may find that they:

- have not been trained to treat a rare cancer with which their patient has been diagnosed.
- do not know what to tell the patient about what to expect with the rare cancer.
- are unable to find an expert who can answer their questions about the rare cancer with which their patient has been diagnosed or identify someone to whom they can refer the patient.

Researchers may find that:

- there is no information about the rare cancer they are investigating to give ideas on how to go about tackling the disease.
- there are no animal or cell models of the rare cancer they are investigating in which to test their ideas.
- there are not enough tumor samples from patients with the rare cancer they are investigating for their research.
- it is hard to find 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 rare cancer research, including the following involving the National Institutes of Health (NIH) and NCI:

The International Rare Cancer Initiative (IRCI)

Established in 2011 by the 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 make it possible 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. To date, the IRCI has convened 12 expert groups and has completed trials in high-grade uterine sarcoma and metastatic anal cancer. Many other clinical trials are underway or planned (385).

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 (386).

Rare Tumor Patient Engagement Network

As part of the Cancer Moonshot, the NIH's 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 network (MyPART), while the NCI Comprehensive Oncology Network Evaluating Rare CNS Tumors (NCI-CONNECT) is studying 12 rare central nervous system cancers in adults.

SANDRA GRIEGO

AGE 61 | COLORADO SPRINGS, COLORADO

Keeping Cancer under Control Thanks to a Clinical Trial

I was diagnosed with a rare type of cancer called epithelioid sarcoma in April 2016. The cancer was causing me immense pain and I could not use my left arm. I was told that I had two options: radical amputation of my whole left shoulder or enroll in a clinical trial testing an oral medication called tazemetostat (Tazverik). I had no hesitation in choosing the clinical trial. I've been taking tazemetostat for a little over 4 years now. The cancer is under control, I have far less pain than I used to, and I have regained some use of my left arm. It has been tough, but I have so much to live for.

In May 2015, I began feeling tingling in my left arm. It felt like pins and needles. Over time, the tingling would last longer and longer. I also began feeling pain in my left shoulder. I eventually went to my primary care physician who referred me for physical therapy.

I had physical therapy for several months, but the pain continued to get worse and worse. I saw an orthopedic specialist, and had many tests of my nerve function, CT scans, and biopsies. In total, it took 11 months before I was diagnosed with stage III epithelioid sarcoma. It turned out that this is a rare type of cancer; the doctors had to send the biopsy to a hospital in Boston to get confirmation of the diagnosis.

At my worst, the pain in my shoulder was so great that I could not use my left arm. I could not use a fork or curl my hair, my husband had to do it for me. I had to hold my left arm up with my right hand and I had to learn to write with my right hand because I am a leftie.

When my oncologist gave me the diagnosis, he brought a whole team with him to explain my treatment options, a surgeon, a nurse practitioner, and a clinical trial coordinator. The surgeon explained that I could have a radical amputation. He pointed to the bump on my neck and said he would have to go and take my whole shoulder out. It sounded absolutely awful. Then, the clinical trial coordinator told me the alternative was a clinical trial testing a new treatment. For that, I would have to take eight tablets a day, four in the morning and four in the evening.

My husband and I were given a few hours to talk before we had to make a decision. It was a no-brainer to choose the clinical trial.

Since July 2016, I have been taking tazemetostat every day. I have a CT scan every 4 weeks and then go to Denver to have blood work done and to see my oncologist. If all looks good, I get another 4 weeks of tablets.

After two or three months, I was excited when the CT scans showed that the tumor had shrunk substantially. It hasn't completely gone, but it hasn't grown either, which is really good. My oncologist says that this is called a partial response and it is a win for patients with epithelioid sarcoma.

For me, the pain has eased a lot; I need far less pain relief than I did. I don't have full use of my left arm, but I get what I need to get done; I am a licensed childcare provider and I currently look after eight children a day.

My experience has taught me that I am a lot stronger than I thought I was, but I could not have done it without the support of my family and friends. My husband takes care of me, two of my sisters each gave up time to stay with me, another sister flies with me to my oncologist appointments; and my neighbor drove me to my appointments for a year. It was hard at first to accept that I needed so much help, but I am so grateful to all of them.

I am also grateful to have had the opportunity to be part of the clinical trial. I do get fatigued, going to bed at 6:30 p.m. some days, but it allowed me to keep my arm. More importantly, I'm alive, and I get to see my son and daughter thrive.

My experience has taught me that I am a lot stronger than I thought I was, but I could not have done it without the support of my family and friends.

do not respond to the molecularly targeted therapeutic and most of those that do initially respond eventually progress because they have become treatment resistant. Two recent FDA decisions are helping to address these challenges.

GISTs fueled by a specific mutation called D842V in a region of the PDGFRA gene known as exon 18 do not respond to imatinib or other FDA-approved molecularly targeted therapeutics (389). Avapritinib (Ayvakit) is a new molecularly targeted therapeutic that can block the effects of D842V mutations. In January 2020, the FDA approved avapritinib for treating adults with metastatic or unresectable GIST that tests positive for any PDGFRA exon 18 mutation, including D842V mutations. The approval was based on results from a phase I clinical trial that showed that 89 percent of patients who had GIST fueled by D842V mutations had complete or partial tumor shrinkage. In a larger group of patients with any mutation in exon 18 of PDGFRA, 84 percent had complete or partial tumor shrinkage.

In May 2020, the FDA approved another new molecularly targeted therapeutic to help address the challenge of treatment resistance, ripretinib (Qinlick). Ripretinib targets KIT and PDGFRα, like imatinib does. It was approved for treating adults with advanced GIST that has progressed despite treatment with three or more other molecularly targeted therapeutics, including imatinib, after it was shown in a phase III clinical trial to dramatically increase the time to disease progression compared with placebo (390).

Tenosynovial giant cell tumors are a group of rare tumors that arise in and around the joints and tendons (391). These tumors are benign, but they cause damage to the joints, which leads to pain, swelling, and limitation of movement of the joint. Surgery is the main treatment option. If patients do not have surgery or if the tumor continually recurs, patients suffer damage and degeneration of the affected joint and surrounding tissues or structures. In some cases, this can cause significant disability.

Research has shown that some cells in tenosynovial giant cell tumors have genetic alterations, called chromosomal translocations, that lead to overproduction of the protein CSF1, which attracts large numbers of immune cells to the site of the tumor. The immune cells that accumulate form the bulk of the tumor and cause damage to surrounding tissue. Pexidartinib (Turalio) is a new molecularly targeted therapeutic that targets the protein that CSF1 attaches to on the surface of immune cells, CSF1R, preventing CSF1 from attaching and, thereby, recruiting the immune cells to the tumor. It was approved by the FDA in August 2019 for treating adults who have a tenosynovial giant cell tumor that is causing them severe morbidity or functional limitations and is not amenable to surgery. The approval was based on results from a phase III clinical trial that showed 38 percent of patients who received pexidartinib had complete or partial tumor shrinkage compared with none of the patients who received placebo (392).

Pexidartinib was the first molecularly targeted therapeutic approved specifically for treating tenosynovial giant cell tumors. In April 2020, patients with another rare type of cancer, cholangiocarcinoma, or bile duct cancer, also gained a first molecularly targeted therapeutic treatment option, pemigatinib (Pemazyre).

Cholangiocarcinoma arises in cells that form the bile ducts, which are small tubes that connect the liver and gallbladder to the small intestine. There are two forms of the disease, named depending on whether the bile ducts in which the cancer begins are inside (intrahepatic cholangiocarcinoma) or outside (extrahepatic cholangiocarcinoma) the liver. Most patients have advanced disease at the time they are first diagnosed with cholangiocarcinoma. Despite treatment with cytotoxic chemotherapy, the prognosis for these patients is poor (393).

Researchers discovered that the growth of up to 20 percent of intrahepatic cholangiocarcinomas is fueled by alterations in the FGFR2 gene (393). Pemigatinib targets FGFR2. It was approved by the FDA for treating adults who have previously treated, unresectable locally advanced or metastatic cholangiocarcinoma that tests positive for an FGFR2 gene alteration using the FoundationOne CDx companion diagnostic. The approval was based on results from a phase II clinical trial that showed that treatment with pemigatinib led to complete or partial tumor shrinkage for 36 percent of patients (394).

Neurofibromatosis type 1 (NF1) is a genetic disorder that causes severe symptoms and complications including a significantly increased risk for developing various types of tumors. Although the tumors that develop in patients with NF1 are usually benign, some patients develop malignant tumors, usually in adolescence or adulthood. Plexiform neurofibromas are tumors that arise in cells that form the covering of peripheral nerves. These benign tumors occur in up to 50 percent of patients with NF1 and can cause pain, disability, and disfigurement. They can also go on to become cancerous.

Research has shown that the growth of plexiform tumors in patients with NF1 is fueled by a signaling pathway that includes proteins called MEK proteins (395). In April 2020, the FDA approved the MEK-targeted therapeutic selumetinib (Koselugo) for treating pediatric patients age 2 and older who have NF1–related plexiform neurofibromas that cannot be safely removed surgically. The approval was based on results from a phase II clinical trial that showed that 66 percent of pediatric patients who received selumetinib had partial tumor shrinkage (395). In addition, many of the children reported experiencing reduced pain, which is one of the most common neurofibroma-related symptoms, along with disfigurement and motor dysfunction.

Kaposi sarcoma arises in the skin; the mucous membranes lining the mouth, nose, and throat; lymph nodes; or other organs. Tumors often arise in more than one place in the body at the same time. They are associated with human herpesvirus-8, also known as Kaposi sarcoma herpesvirus.

There are several types of Kaposi sarcoma. The most common type in the United States is epidemic Kaposi sarcoma, also known as AIDS-related Kaposi sarcoma. Treating patients who have HIV with highly active antiretroviral therapy (HAART) often keeps Kaposi sarcoma at bay, but not always. In May 2020, the FDA expanded the use of a molecularly targeted therapeutic previously approved for treating multiple myeloma, pomalidomide (Pomalyst), to help address this challenge. Pomalidomide works against cancer in several ways, including by modulating aspects of the immune system and by reducing the production of molecules called VEGFs, which leads to disruption of new blood and lymphatic vessel networks. It was approved by the FDA for treating adults who have AIDS-related Kaposi sarcoma after failure of HAART and Kaposi sarcoma in adult patients who are HIV-negative after it was shown in a phase I/II clinical trial to cause partial or complete tumor shrinkage for 67 percent of HIV-positive patients and 80 percent of HIV-negative patients (396).

Advancing Bladder Cancer Treatment

Bladder cancer is the sixth most commonly diagnosed cancer in the United States, with more than 81,000 new cases expected to be diagnosed in 2020 (5).

More than 90 percent of bladder cancers diagnosed in the United States are classified as urothelial cancers because they arise in cells that comprise the transitional cell urothelium that lines the bladder. Research has shown that up to 60 percent of bladder cancers are characterized by elevated levels of a protein called nectin-4 (397).

Enfortumab-vedotin-ejfv is an antibody-drug conjugate that comprises a cytotoxic agent, monomethyl auristatin E, attached to a nectin-4–targeted antibody by a linker. When the antibody attaches to nectin-4 on the surface of bladder cancer cells, the antibody-drug conjugate is internalized by the cells. This leads to monomethyl auristatin E being released from the linker and antibody. Once free, the monomethyl auristatin E is toxic to the bladder cancer cells, which ultimately die.

In December 2019, the FDA approved enfortumab vedotin-ejfv for treating adults who have locally advanced or metastatic urothelial cancer that has progressed despite treatment with an immune checkpoint inhibitor and a platinum-containing cytotoxic chemotherapy regimen. The approval was based on results from a phase II clinical trial that showed that 44 percent of patients had complete or partial tumor shrinkage after treatment with enfortumab vedotin-ejfv (398).

Treatment with Immunotherapy

Cancer immunotherapy refers to the use of therapeutics that unleash the power of a patient's immune system to fight cancer. Not all these therapeutics, which are known as immunotherapeutics, work in the same way (see sidebar on **How Immunotherapeutics Work,** p. 100).

In the past decade, cancer immunotherapy emerged as the fifth pillar of cancer care (see **Figure 14,** p. 75). It is one of the most exciting approaches to cancer treatment to have ever entered the clinic. This is in part because some of the patients with metastatic disease who have been treated with these revolutionary treatments have had remarkable and durable responses, as **Dr. Al Stroberg** has had after being treated with ipilimumab almost 10 years ago because he had advanced melanoma (see p. 98). Unfortunately, only a minority of patients have such incredible responses. In addition, the current FDA-approved immunotherapeutics do not work against all types of cancer. Identifying ways to increase the number of patients for whom treatment with an immunotherapeutic yields a remarkable and durable response is an area of intensive basic and clinical research investigation.

Fortunately, our scientific understanding of the immune system and how it interacts with cancer cells is rapidly increasing, and there are already clinical trials underway testing many novel immunotherapeutics and testing new ways to use those that we already have (399)(400). The new immunotherapeutics and treatment strategies that are on the horizon hold extraordinary promise for the future. Here, however, we focus on new immunotherapeutics that were approved by the FDA in the 12 months covered by this report, August 1, 2019 to July 31, 2020, and previously approved immunotherapeutics that were approved for use against additional types of cancer during the same period (see **Table 6,** p. 74).

Releasing the Brakes on the Immune System

Research has shown that immune cells called T cells are naturally capable of destroying cancer cells. It has also shown that some 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. These brakes, which are proteins on the surface of T cells, are called immune-checkpoint proteins.

This knowledge led researchers to develop therapeutics that release certain T-cell brakes, freeing the T cells to destroy the cancer cells. These immunotherapeutics are called checkpoint inhibitors (see **Figure 17,** p. 101).

As of July 31, 2020, there are seven checkpoint inhibitors approved by the FDA. Ipilimumab, which was the first of these immunotherapeutics to be approved by the FDA, in March 2011, targets the immune-checkpoint protein CTLA-4.

DR. AL STROBERG
AGE 71 | OJAI, CALIFORNIA

Surviving Long after a Melanoma Diagnosis Thanks to Ipilimumab

By early 2011, melanoma had spread widely through my body despite surgery, radiotherapy, and several other treatments. I was so sick that my sons came home and we began preparing my wake. Then, on Father's Day 2011, not long after my second infusion with a new treatment called ipilimumab (Yervoy), I began noticing an improvement in my condition. After that, I had just one more infusion with ipilimumab, my tumors shrank and, ultimately, they disappeared. That was more than nine years ago, and I'm now enjoying life with no sign of cancer.

My journey with cancer began back in 2005, when I noticed a lump on my neck. It turned out to be non-Hodgkin lymphoma. I was lucky; chemotherapy and an immunotherapy called rituximab (Rituxan) cleared it up and I was able to return to my work as an orthopedic surgeon at UCLA.

A few years later, I noticed another lump under my chin. I immediately thought it must be a recurrence of the non-Hodgkin lymphoma and returned to my oncologist at UCLA. To my surprise, and the surprise of my oncologist, a biopsy of the lump showed that it was melanoma, not non-Hodgkin lymphoma.

After numerous tests and scans, it was determined that the melanoma had originated in a freckle on my right cheek and spread to some of the lymph nodes in my neck. I had an eight-hour operation during which the surgeon removed the original tumor on my cheek and 27 lymph nodes in my neck. Analysis of the lymph nodes showed that 25 of them were positive for melanoma; the surgeon told me that he had never seen a melanoma so widespread before.

Given the extent of the disease, I had two months of radiotherapy aimed at my head and neck during spring 2010. Unfortunately, this did not stop the melanoma from spreading, and so I started a course of interferon, which boosts the immune system. The goal of the treatment was to boost the immune system enough that it would attack the melanoma, but it did not work for me and I experienced the intense flu-like symptoms that are side effects of interferon treatment.

We then tried a chemotherapy called Abraxane. Again, this did nothing to slow the spread and growth of the melanoma. I did lose my hair and have peripheral neuropathy in my hands and feet, which made it hard to tie my shoes and button my shirts.

At this point, I was very sick. I had lost 40 pounds. I couldn't climb the stairs. I spent 18 or 19 hours of the day in bed because I could barely move. Fluid began to accumulate around my lungs, a condition called pleural effusion, which made it hard for me to breathe. At first, I had to go to the hospital regularly to have the fluid drawn from around the lungs. Later, a surgeon placed a tube in my chest so that my wife and I could drain the fluid at home.

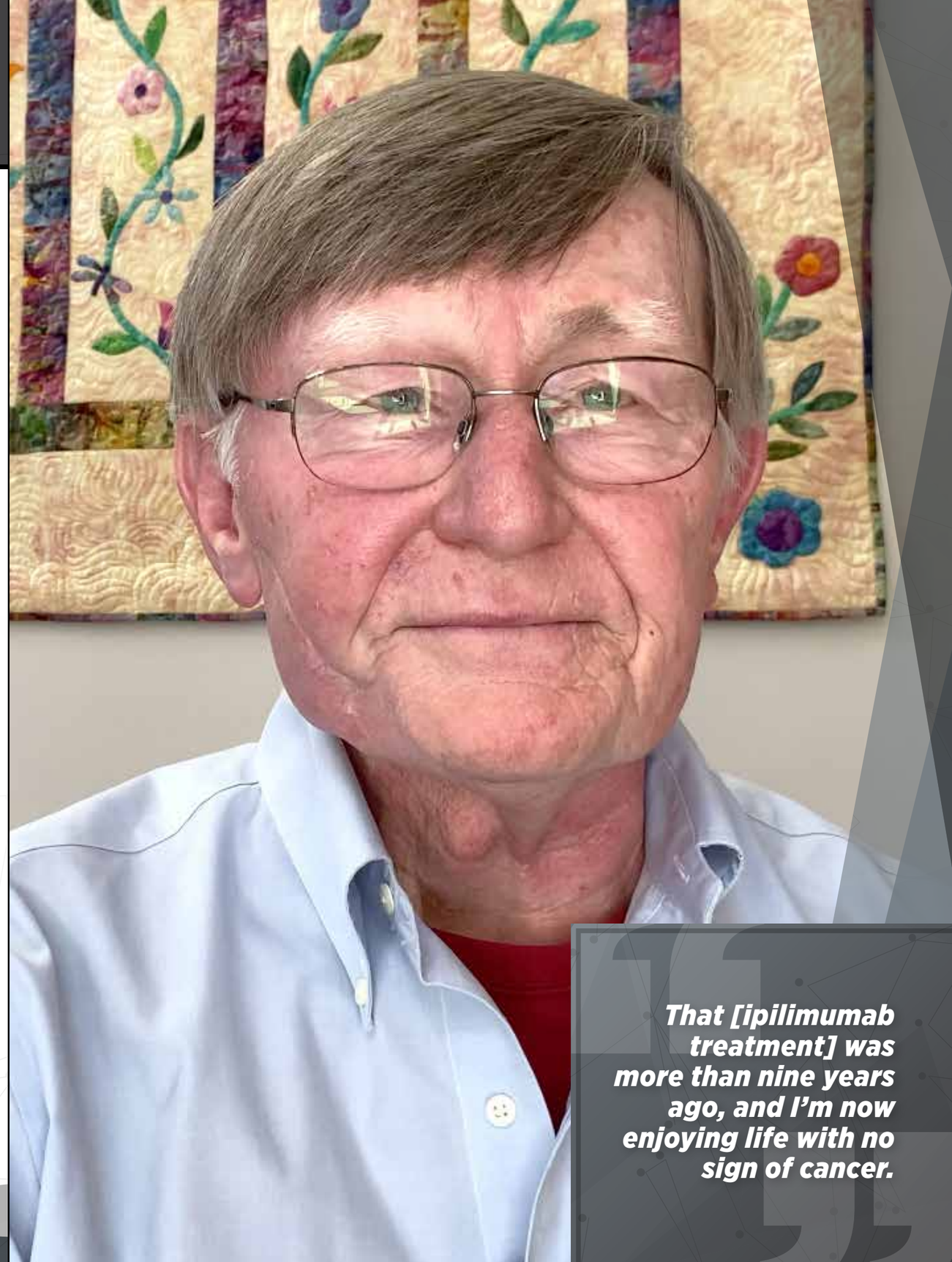
My oncologist knew of a new type of treatment, an immunotherapy called ipilimumab, that was being reviewed by the U.S. Food and Drug Administration (FDA) and that he believed might help me. It was approved on March 25, 2011, and I received my first infusion a few weeks after that.

My condition didn't seem to change after the first infusion of ipilimumab, and I was sure I was going to die. My sons came home to say their goodbyes. Then, just after the second ipilimumab infusion, I noticed that the amount of fluid we were drawing off the lungs every day started to decrease and a large lump on my right shoulder began decreasing in size.

By the third ipilimumab infusion, there was no fluid to draw off my lungs. My next scan showed the cancer was disappearing. We drove the children back to the airport so that they could go back to school and get on with their lives.

Today, the scans continue to show no sign of melanoma, and I am immensely grateful for the basic research that led to the development of treatment that saved my life. Ipilimumab works by taking the brakes off immune cells called T cells. In 1974, when I was in medical school, I spent several months in a basic research laboratory that was at the forefront of T-cell research. Work like that was built upon over the years by many researchers, including Jim Allison, and led to ipilimumab.

We need the federal government to invest in research because this will drive progress against cancer in the future. There is nothing more important than that for our children and grandchildren.



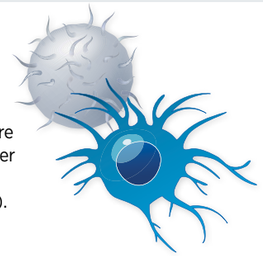
That [ipilimumab treatment] was more than nine years ago, and I'm now enjoying life with no sign of cancer.

HOW IMMUNOTHERAPEUTICS WORK

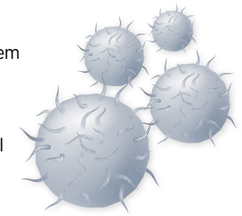
The way in which different immunotherapeutics unleash a patient's immune system to fight cancer varies:

Some release the brakes on the natural cancer-fighting power of the immune system, for example, ipilimumab (Yervoy), durvalumab (Imfinzi), nivolumab (Opdivo), and pembrolizumab (Keytruda) (see **Releasing the Brakes on the Immune System, p. 97**).

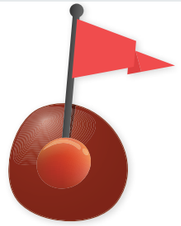
Some enhance the cancer-killing power of the immune system by triggering cancer-fighting T cells; these are called therapeutic cancer vaccines, for example, sipuleucel-T (Provenge).



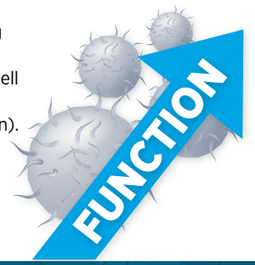
Some amplify the killing power of the immune system by providing more cancer-targeted immune cells called T cells, for example, brexucabtagene autoleucel (Tecartus), axicabtagene ciloleucel (Yescarta) and tisagenlecleucel (Kymriah).



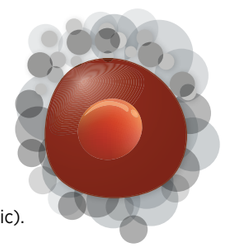
Some flag cancer cells for destruction by the immune system, for example mogamulizumab-kpkc (Poteligeo).



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).



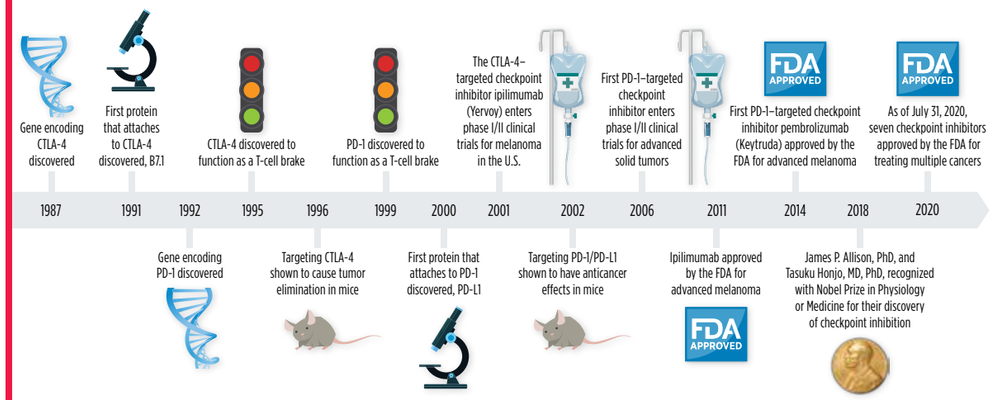
Adapted from (1)

Ipilimumab protects CTLA-4 from the proteins that attach to it and trigger it to put the brakes on cancer-cell killing by T cells. The other six FDA-approved checkpoint inhibitors release a different T-cell braking system. They target either the immune-checkpoint protein PD-1 or PD-L1, which is one of the proteins that applies the PD-1 brake on T cells.

Checkpoint inhibitors have broad utility in the treatment of cancer; most of these groundbreaking immunotherapeutics are approved by the FDA for treating multiple types of cancer (see **Figure 18,** p. 106). During the 12 months spanning this report, August 1, 2019 to July 31, 2020, the FDA approved expanding the uses of five of the checkpoint inhibitors—atezolizumab (Tecentriq), durvalumab (Imfinzi), ipilimumab, nivolumab, and pembrolizumab—to include the treatment of additional types of cancer. These approvals mean that as of July 31, 2020, one or more checkpoint inhibitor were approved for treating 16 types of cancer and for treating any type of solid tumor characterized by the presence of certain molecular characteristics, microsatellite instability–high, DNA mismatch–repair deficiency, and tumor mutational burden–high.

One of the expanded uses for PD-1/PD-L1–targeted checkpoint inhibitors approved by the FDA during the 12 months spanning this report was the June 2020 approval of pembrolizumab for treating certain adults and children with solid tumors characterized by the presence of a specific molecular characteristic, or biomarker, called tumor mutational burden–high. These biomarkers are found in

FIGURE 17 STOPS ALONG THE WAY TO DEVELOPING 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 to be 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 to be approved by the FDA was pembrolizumab (Keytruda), in September 2014. More than 20 years of 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 (401) (402). Other basic research milestones along the way to the FDA approvals include the identification of the brake function of CTLA-4 and PD-1 (403) (404)(405), identification of the proteins that attach to and trigger the brake function of CTLA-4 and PD-1 (406)(407), and the demonstration that immunotherapeutics targeting these brakes can protect them from being triggered (402) (408). 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."

Adapted from (409)

a proportion of cancers arising at numerous sites in the body, including melanoma and lung cancer (410). This is the second FDA approval of pembrolizumab based on a common biomarker and not the location in the body where the cancer originated (see **Figure 19,** p. 107).

The approval was based on data from a phase II clinical trial showing that pembrolizumab treatment led to tumor shrinkage in about 30 percent of patients with an unresectable or metastatic, tumor mutational burden–high solid tumor that had progressed despite prior treatment. The patients included in the analysis had been shown to have tumors that were tumor mutational burden–high using the FoundationOneCDx assay companion diagnostic, which the FDA approved for identifying patients eligible for pembrolizumab treatment. Thus, the approval provides new treatment options and new hope to patients with a wide range of types of cancer, like **Leonard Ganz** who has urothelial carcinoma and **Barbara Bigelow** who has triple-negative breast cancer (see p. 102 and p. 104).

The other biomarkers that can be used to identify patients with solid tumors that have progressed after prior treatment and who are now eligible for treatment with pembrolizumab are microsatellite instability–high and DNA mismatch–repair deficiency (30). About 15 percent of the colorectal cancer cases diagnosed in the United States are characterized by these biomarkers (411). The use of pembrolizumab was expanded in July 2020 to include the initial treatment of patients with colorectal cancer that is characterized by either

LEONARD GANZ

AGE 77 | EDGEWATER, NEW JERSEY

Maintaining a Positive Attitude with Immunotherapy

I was diagnosed with metastatic urothelial carcinoma in May 2012. Surgery was the only treatment that I needed for the metastasis until January 2019, when the tumor in my lung recurred. After chemotherapy had no effect, I was told my tumor had a high mutational burden and that made me a great candidate for a clinical trial testing an immunotherapy treatment called pembrolizumab (Keytruda). In the 11 months since I started on the trial, the tumor has shrunk dramatically. My wife and I are overwhelmed by the results, and we couldn't be more thankful for all the research that made this possible.

My journey with urothelial cancer is complicated. In September 2010, my primary care physician suggested that I see a prostate specialist because of enlargement to my prostate and an elevated level of PSA. I was diagnosed with prostate cancer. After researching the treatment options, my wife Roberta and I decided that I would have prostate surgery. During the pre-op testing for the prostate surgery, the doctors discovered a blockage in my ureter [the tube in which urine passes from the kidney to the bladder]. Further tests showed that it was urothelial cancer.

After I had recovered from the prostate surgery, Roberta and I saw several urologists to get opinions on the best treatment for the urothelial cancer. The opinions varied widely, but we opted for laser ablation of the blockage. After three laser ablations did not eliminate the tumor, I was treated with a chemotherapy called mitomycin. The chemotherapy was administered into my kidney from which it dripped through the ureter, contacting the tumor. The treatments were long and painful.

Then, in May 2012, a CAT scan showed that the urothelial cancer had spread to the tip of my right lung. The metastasis was removed during a wedge surgery. At this point, my urologist recommended that I transfer my care to an oncologist. I needed no further treatment until January 2019, when it was discovered that the tumor in my lung had recurred.

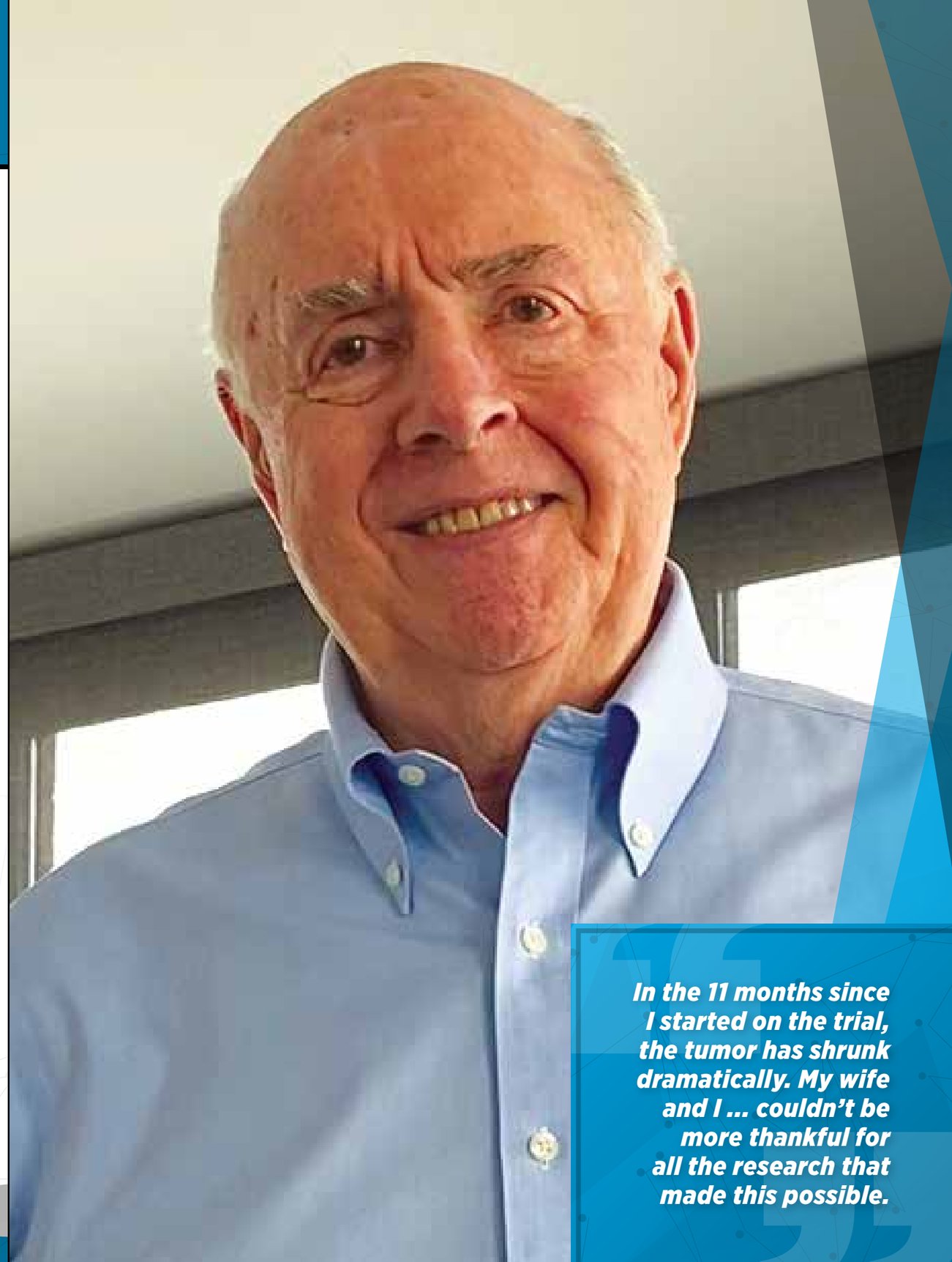
At this point, a sample of the tumor in my lung was tested for a number of biological and genetic characteristics. I was told that the tumor was not positive for PD-L1 so I was not eligible for immunotherapy. My only treatment option was chemotherapy. I received gemcitabine and carboplatin for five months. The tumor did not grow, but it did not shrink either. As a result, the chemotherapy was deemed ineffective.

The oncologist knew from the genetic analysis that the mutational load of the tumor was very high. In fact, I was told it was the highest he had ever seen. Because of this and the fact that chemotherapy was ineffective, I was offered the chance to participate in a clinical trial testing the immunotherapy pembrolizumab.

Roberta and I are big believers in science and medicine, and we jumped at the chance for me to join the clinical trial. For the past 11 months, I have been having an infusion of pembrolizumab every three weeks and CAT scans every two months. The results have been fabulous, and I am extremely thankful to be part of this clinical trial. The tumor has shrunk dramatically, and the oncologist is extremely pleased with the results, but he has recommended that I complete the clinical trial and then we will assess what treatment I need, if any.

The incredible results I have seen with pembrolizumab have outweighed the disappointment that I felt when the chemotherapy was ineffective. I choose to keep a very positive outlook and to move forward with my life; there is a lot to be grateful for.

We need to make sure that Congress continues to fund the research that makes possible the advances like the one that I am benefiting from.



In the 11 months since I started on the trial, the tumor has shrunk dramatically. My wife and I ... couldn't be more thankful for all the research that made this possible.

BARBARA BIGELOW

AGE 62 | BUZZARD'S BAY, MASSACHUSETTS

Enjoying Life Because of Cancer Research

Almost 13 years after my initial diagnosis with stage II ER-positive breast cancer, the cancer metastasized. A biopsy of a metastasis in my liver showed that the cancer was now triple-negative, that it had a high tumor mutational burden, and that it was high for PD-L1. This knowledge turned my treatment plan on its head; I enrolled in a clinical trial testing a combination of an immunotherapy and a chemotherapy. The side effects made me so sick that I was in a medically induced coma for 10 days, but the metastases were eliminated and there has been no evidence of the cancer for 4½ years. I am grateful to be alive, enjoying life with my husband, daughters, and new grandson.

My long journey with breast cancer started when I was 44. I went for a routine mammogram, but nothing was routine about it; immediately after the mammogram, they performed an ultrasound and biopsy. The following day, my husband's birthday, I was told that I had stage II ER-positive cancer.

I began treatment with breast-conserving surgery. I found out after the surgery that the cancer had spread to some of my lymph nodes, which was heartbreaking. I then had radiotherapy and chemotherapy with doxorubicin and cyclophosphamide. It was a really tough year. I had so many side effects; I was anemic, I had to have blood transfusions, I lost my hair. One of my sisters also passed away from breast cancer.

After the chemotherapy, I took anastrozole, an antihormone treatment, for 10 years to reduce the risk of the cancer recurring. I also had my ovaries removed and a bilateral mastectomy with reconstruction to further reduce my risk of recurrence.

About three years after I finished the anastrozole treatment, I was experiencing a worsening of back pain that I had been suffering for a while. An MRI ordered by my back surgeon showed not only back issues, but also an area of concern near my right kidney, which turned out to be a tumor; I had stage IV breast cancer.

I was devastated. I started taking palbociclib and letrozole, but PET scans six months later, in September 2015, showed that the disease had progressed further and was now in my liver as well.

At this point, I sought a second opinion at Dana Farber Cancer Institute. The oncologist I met was wonderful, and I switched my care immediately. I took fulvestrant, another antihormone treatment, for three months, but again the cancer kept progressing; I had seven tumors in my liver, the base of my spine, and lymph nodes.

A biopsy of one of the liver metastases showed why the treatments had not stopped the cancer from progressing; the cancer was no longer ER-positive. I was now faced with a diagnosis of metastatic triple-negative breast cancer, a very aggressive disease.

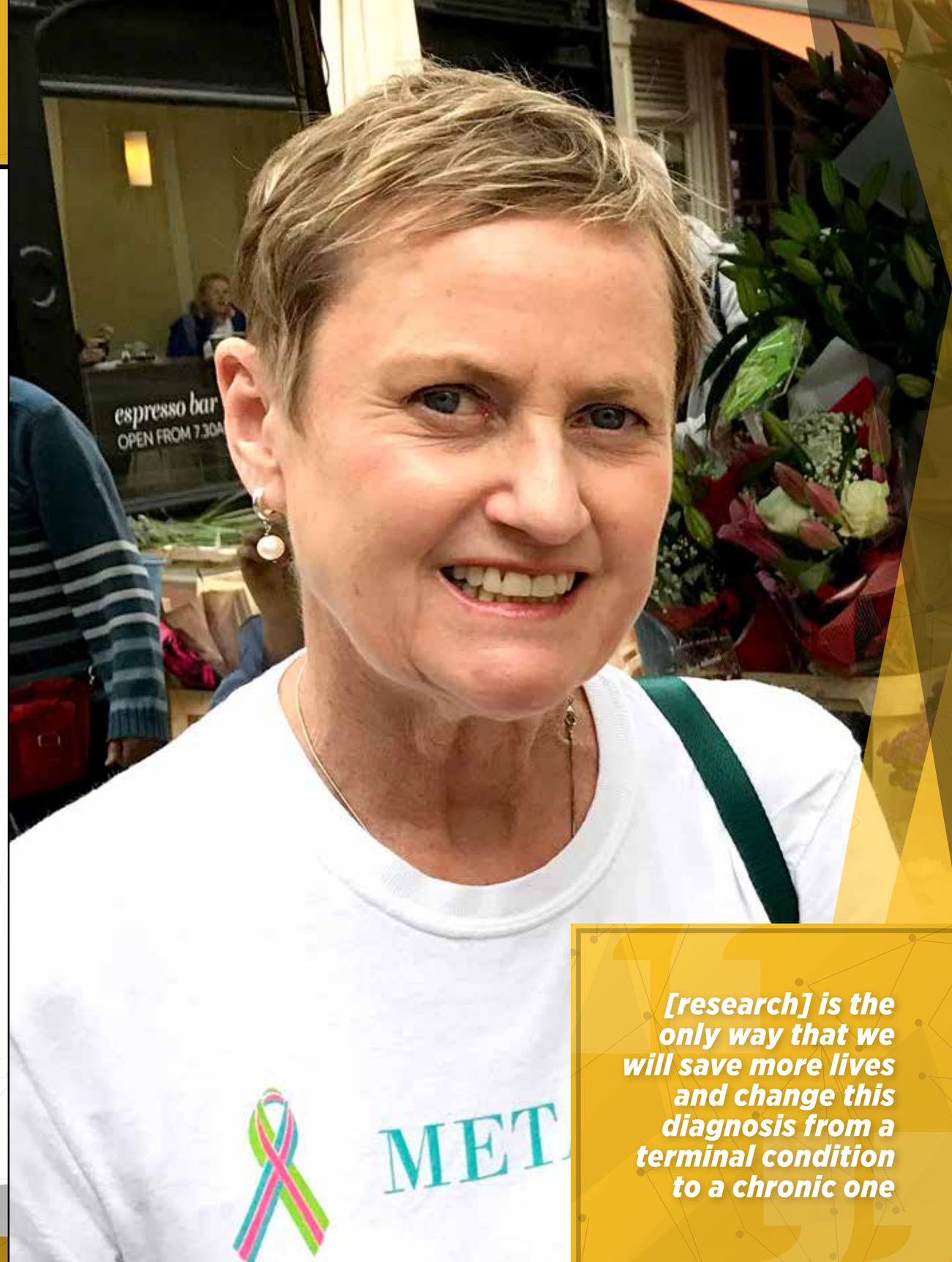
My oncologist told me that my cancer had a high tumor mutational burden and was high for PD-L1, which made me a good candidate for immunotherapy. I enrolled in a clinical trial testing the immunotherapy pembrolizumab (Keytruda) in combination with the chemotherapy eribulin.

I knew the treatment would be aggressive, so I was prepared when I started losing weight, vomiting daily, and losing my hair. I struggled on for about three months. Then, the skin around the port through which the chemotherapy was delivered to my body became red and looked infected. At the emergency room, I was given antibiotics and sent home. A few days later, I developed a high fever and started vomiting. By the end of the day I had been admitted to the intensive care unit (ICU).

In the ICU, I started going downhill fast. I was placed in a medically induced coma and given a less than 10 percent chance of surviving. Eventually, the doctors determined that I did not have an infection, I had hyperinflammatory syndrome as a result of the pembrolizumab. They started me on steroids to counteract the inflammation, and my condition began improving slowly. When I was woken from the coma, I had lost 42 pounds and my muscles had atrophied. I had to spend a month in the hospital and then a month in an acute rehabilitation facility learning to walk, talk, eat, and look after myself again.

Despite this horrific experience, scans showed no evidence of the breast cancer. It has remained that way ever since. I do have some significant long-term effects from the treatments I have received, including adrenal insufficiency and balance problems. But I am alive; I did not think I would live to see my oldest daughter graduate from college, let alone get married and have a child. My husband and I are so happy enjoying magical moments together.

I also devote a lot of time and energy into raising awareness about metastatic breast cancer and the need for funding for research into the disease. It is the only way that we will save more lives and change this diagnosis from a terminal condition to a chronic one.



[research] is the only way that we will save more lives and change this diagnosis from a terminal condition to a chronic one

FIGURE 18 GOING DEEP WITH CHECKPOINT INHIBITORS

FDA-Approved as of July 31, 2020

Hodgkin lymphoma: nivolumab and pembrolizumab

Non-Hodgkin lymphoma: pembrolizumab

Esophageal cancer: nivolumab and pembrolizumab

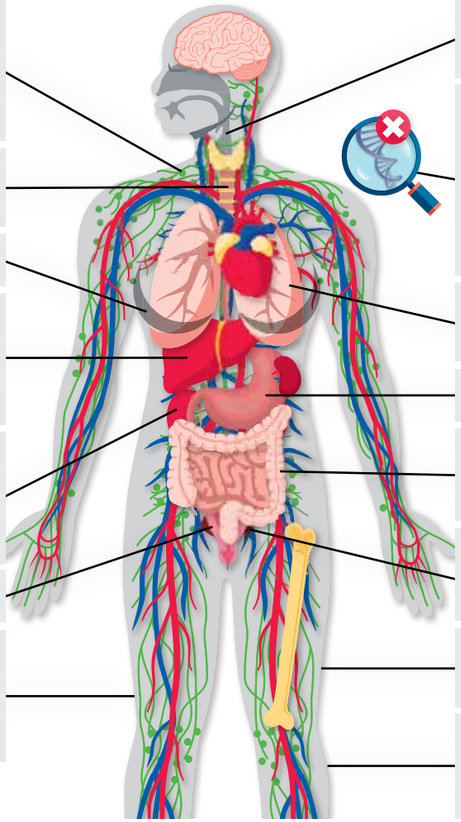
Breast cancer: atezolizumab

Liver cancer: Atezolizumab, nivolumab, pembrolizumab and combination of ipilimumab and nivolumab

Kidney cancer: avelumab, nivolumab, pembrolizumab, and combination of ipilimumab and nivolumab

Cervical cancer: pembrolizumab

Melanoma: Atezolizumab, ipilimumab, nivolumab, pembrolizumab, and combination of ipilimumab and nivolumab



Head and neck cancer: nivolumab and pembrolizumab

Solid tumors that are microsatellite instability–high or mismatch repair–deficient: pembrolizumab

Solid tumors that are tumor mutational burden-high: pembrolizumab

Lung cancer: atezolizumab, durvalumab, nivolumab, pembrolizumab and combination of ipilimumab and nivolumab

Gastric cancer: pembrolizumab

Colorectal cancer: nivolumab and combination of ipilimumab and nivolumab

Bladder cancer: atezolizumab, avelumab, durvalumab, nivolumab, and pembrolizumab

Merkel cell carcinoma: avelumab and pembrolizumab

Cutaneous squamous cell carcinoma: cemiplimab-rwlc and pembrolizumab

Checkpoint inhibitors are cancer immunotherapeutics that work by releasing "brakes" on the surface of immune cells called T cells, which are naturally capable of destroying cancer cells. The first checkpoint inhibitor to be approved by the U.S. Food and Drug Administration (FDA) was ipilimumab (Yervoy), in March 2011, for metastatic melanoma. Three and a half years passed before another checkpoint inhibitor was approved, pembrolizumab (Keytruda), again for metastatic melanoma. Since then, another five checkpoint inhibitors have been approved by the FDA, atezolizumab (Tecentriq), avelumab (Bavencio), cemiplimab-rwlc (Libtayo), durvalumab (Imfinzi), and nivolumab (Opdivo). In addition, the 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, 2020, one or more checkpoint inhibitors were approved for treating 16 types of cancer and for treating any type of solid tumor characterized by the presence of certain molecular characteristics, 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 deep selection of checkpoint inhibitors available as treatment options.

Adapted from (212)

FIGURE 19 MORE PRECISELY IDENTIFYING TUMORS LIKELY TO RESPOND TO CHECKPPOINT INHIBITORS

Tumor does not have "high mutational burden"

Tumor is "tumor mutational burden (TMB)-high"

Precision medicine is broadly defined as treating a patient based on characteristics that distinguish that patient from other patients with the same disease. The U.S. Food and Drug Administration (FDA) approval of pembrolizumab (Keytruda) for the treatment of any solid tumor identified to be tumor mutational burden–high is an example of precision immunotherapy. The scientific rationale underpinning this approval was the result of the dedicated researchers integrating scientific discoveries in the fields of immunology and cancer biology to develop an understanding of why tumor mutational burden–high is an effective biomarker for the use of pembrolizumab. Cancer cells with this biomarker have a much higher number of mutations in their DNA compared with other cancer cells (in the case of this approval it was measured using a defined test as 10 or more mutations per megabase of DNA). These mutations give rise to altered proteins, which are recognized as abnormal, or foreign, to cancer-fighting immune cells called T cells. These T cells are spurred into action when the PD-1 brake that is preventing them from eliminating cancer cells is released by pembrolizumab. In cancer cells that are not tumor mutational burden–high, the dramatically fewer DNA mutations mean fewer altered proteins. The immune cells in this situation accept the protein landscape in the tumor as normal and are unlikely to be spurred into action by pembrolizumab.

Adapted from (30)

microsatellite instability–high or DNA mismatch–repair deficiency. The approval was based on results from a phase II clinical trial that showed that the time before disease progression was almost double among patients who received pembrolizumab compared with patients who received standard treatments.

Endometrial cancer is another type of cancer that is frequently characterized by microsatellite instability–high and DNA mismatch–repair deficiency. In September 2019, however, the FDA expanded the use of pembrolizumab to include the treatment of women who have advanced endometrial cancer that is neither microsatellite instability–high nor mismatch repair–deficient and who have disease progression following prior systemic therapy but are not candidates for curative surgery or radiation. When being used in this way, pembrolizumab should be used in combination with the molecularly targeted therapeutic lenvatinib (Lenvima). The approval was based on data from a phase I/II clinical trial showing that pembrolizumab and lenvatinib treatment led to tumor shrinkage in about 40 percent of patients (412).

In June 2020, the FDA also added cutaneous squamous cell carcinoma as a type of cancer for which pembrolizumab is an approved treatment option. Most patients diagnosed with this type of skin cancer are cured by surgery and/or radiation. However, in some cases, the disease does advance, and pembrolizumab was approved to help address this challenge. The approval of pembrolizumab for treating patients with recurrent or metastatic cutaneous squamous cell carcinoma that is not curable by surgery or radiation was

based on results from a phase II clinical trial that showed that 34 percent of patients who received the immunotherapeutic had complete or partial tumor shrinkage.

Durvalumab is another PD-1/PD-L1–targeted checkpoint inhibitor to have its use expanded to a new type of cancer by the FDA in the 12 months spanning this report. In March 2020, the FDA approved the checkpoint inhibitor for use in combination with two cytotoxic chemotherapeutics—etoposide and either carboplatin or cisplatin—for the initial treatment of certain patients with advanced SCLC. The approval was based on results from a phase III clinical trial that showed that adding durvalumab to standard cytotoxic chemotherapy improved overall survival (413).

The use of nivolumab was also expanded during the 12 months spanning this report. In June 2020, it was approved for treating certain adults who have advanced, recurrent, or metastatic, squamous cell carcinoma of the esophagus that has progressed despite cytotoxic chemotherapy. Although esophageal cancer is a rare type of cancer, which is expected to be a diagnosis received by 18,440 people in the United States in 2020, it is also one of the deadliest; the 5-year relative survival rate for patients diagnosed with the disease is just 20 percent (2). The approval was based on results from a phase III clinical trial in which it was shown that nivolumab improved overall survival compared with standard cytotoxic chemotherapy (414).

Nivolumab has been previously approved by the FDA as a treatment for NSCLC and hepatocellular carcinoma, which is the most common type of liver cancer. These approvals, which were granted in March 2015 and September 2017, respectively, yielded remarkable and durable responses for only some patients and the 5-year relative survival rates for those diagnosed with these types of cancer at an advanced stage remain below 20 percent (2). Thus, researchers are testing various ways to increase the number of patients who benefit from nivolumab, including evaluating how well it works in combination with other immunotherapeutics. In March 2020, the FDA approved using nivolumab in combination with ipilimumab to treat patients with hepatocellular carcinoma that has progressed after standard treatment when it was shown in a phase I/II clinical trial to cause tumor shrinkage in 33 percent of patients. In May 2020, the same combination of checkpoint inhibitors was approved by the FDA for treating patients who have NSCLC that express at least 1 percent PD-L1, as measured using the PD-L1 IHC 28-8 pharmDx companion diagnostic, and that are not fueled by mutations in either the EGFR gene or the ALK gene. This approval for NSCLC was based on results from a phase III clinical trial in which it was shown that the combination improved overall survival compared with platinum-based cytotoxic chemotherapy (415).

The fifth checkpoint inhibitor to have its use expanded by the FDA during the 12 months spanning this report is atezolizumab. In May 2020, it was approved for use in combination with a molecularly targeted therapeutic called bevacizumab (Avastin) as a new initial treatment for patients with hepatocellular carcinoma that cannot be removed by surgery or metastatic hepatocellular carcinoma. Most patients who receive these diagnoses are initially treated with the molecularly targeted therapeutic sorafenib (Nexavar). Unfortunately, the majority of those whose tumors initially respond to this treatment eventually have disease progression, highlighting the need for new, more effective treatment options. The atezolizumab–bevacizumab combination was approved by the FDA after it was shown in a phase III clinical trial to improve overall survival compared with sorafenib (416).

In July 2020, the FDA further expanded the use of atezolizumab to include melanoma, which is the deadliest type of skin cancer. This approval is for the use of atezolizumab in combination with two molecularly targeted therapeutics, cobimetinib (Cotellic) and vemurafenib (Zelboraf), which were approved for treating melanoma fueled by mutations in the BRAF gene called V600 mutations in November 2015 (57). The new combination of atezolizumab, cobimetinib, and vemurafenib was approved for treating patients with melanoma that is metastatic or cannot be removed by surgery and that tests positive for a BRAF V600 mutation. The approval was based on results from a phase III clinical trial in which it was shown that adding atezolizumab to cobimetinib and vemurafenib significantly increased the time before disease progression (417).

Even though checkpoint inhibitors have yielded extraordinary benefit for patients with a diverse array of cancer types, not all patients have tumors that respond to these immunotherapeutics and many whose tumors do respond, initially, develop resistance after a while. Therefore, researchers are working hard to determine how to increase the number of patients who benefit from these lifesaving immunotherapeutics, as discussed in **Expanding the Scope of Checkpoint Inhibitors** (p. 125).

Increasing the Cancer-killing Capacity of the Immune System

In some patients with cancer, it is not an issue of T-cell brakes being triggered that prevents the patient's immune system attacking and destroying the cancer cells; rather, it is an issue of there being insufficient cancer-killing T cells.

One of the most recently developed ways to dramatically increase the number of functional cancer-killing T cells that a patient has is an approach to immunotherapy called adoptive T-cell therapy (418). Adoptive T-cell therapy is a complex medical procedure that is customized for each patient. During treatment, T cells are harvested from a patient, expanded in number and/or genetically modified in the laboratory, and then returned to the patient, where they attack and potentially eliminate the cancer cells (see sidebar on **Types of Adoptive T-Cell Therapy,** p. 109).

In July 2020, the FDA approved a third adoptive T-cell therapy, brexucabtagene autoleucel (Tecartus). Similar to the first two of these revolutionary new types of immunotherapy approved by the FDA—axicabtagene ciloleucel (Yescarta) and tisagenlecleucel (Kymriah)—it is categorized as chimeric antigen receptor (CAR) T-cell therapy. Given that CAR T-cell therapy involves genetic modification of a patient's cells, it is sometimes referred to as cell-based gene therapy. For all three of the CAR T-cell therapies approved by the FDA, a patient's T cells are genetically modified to have a CAR that targets the molecule CD19.

CD19 is a protein found on the surface of immune cells called B cells. Several types of leukemia and lymphoma arise in B cells, including an aggressive type of non-Hodgkin lymphoma called mantle cell lymphoma.

The latest estimates show that the mantle cell lymphoma incidence rate has been increasing steadily since the turn of the century (420). There are now more than 3,300 new cases of the disease diagnosed in the United States each year. Brexucabtagene autoleucel was approved for treating adults who have mantle cell lymphoma that has not responded to or that has relapsed following at least one other treatment. The approval was based on results from a phase II clinical trial that showed that more than 60 percent of patients who received brexucabtagene autoleucel had complete responses, meaning no cancer was detectable during at least one follow-up examination (421).

Like the other CAR T-cell therapies, brexucabtagene autoleucel can sometimes cause severe or life-threatening cytokine-release syndrome and other serious adverse effects, including potentially life-threatening swelling in the brain. Therefore, the FDA has put in place a risk evaluation and mitigation strategy that requires that health care facilities using brexucabtagene autoleucel be specially certified. Researchers also are working hard to identify new ways to reduce the severe adverse effects of CAR T-cell therapies without decreasing the therapeutic benefit of these immunotherapeutics.

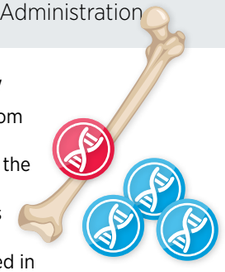
Directing the Immune System to Cancer Cells

An immune cell must find a cancer cell before it can destroy it. Many immunotherapeutics that have been approved by the FDA for treating cancer work, at least in part, by helping immune cells find cancer cells (see **Cell Lysis Mediators** in **Supplemental Table 2,** p. 165). The most recent additions to this group of immunotherapeutics are isatuximab-irfc (Sarclisa), which was approved by the FDA in March 2020 for treating certain patients with multiple myeloma, and tafasitamab-cxix (Monjuvi), which was approved by the FDA in July 2020 for treating certain patients with diffuse large B-cell lymphoma.

TYPES OF ADOPTIVE T-CELL THERAPY

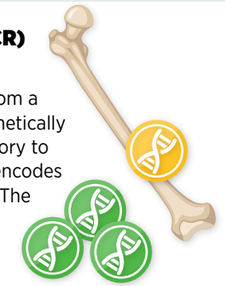
There are three main types of adoptive T-cell therapy (419). As of July 31, 2020, only one type, chimeric antigen receptor (CAR) T-cell therapy, is approved by the U.S. Food and Drug Administration.

CAR T-Cell Therapy



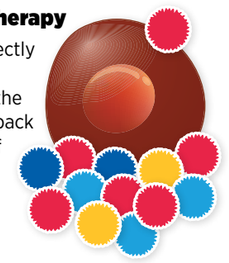
T cells are harvested from a patient's blood and genetically modified in the laboratory to have a new gene that encodes a protein called a CAR. The T cells are expanded in number and infused back into the patient. The CAR modification targets the T cells specifically to the patient's cancer cells and triggers them to attack when they get there.

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 and triggers them to attack when they get there.

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.

Adapted from (212)

Multiple myeloma is one of the most commonly diagnosed blood cancers in the United States, with 32,270 new cases expected to be diagnosed in 2020 (5). In recent years, the development and FDA approval of new therapeutics—including proteasome inhibitors like bortezomib (Velcade) and carfilzomib (Kyprolis), immunomodulatory agents like lenalidomide (Revlimid) and pomalidomide, and immunotherapeutics like the CD38-targeted daratumumab (Darzalex)—have improved outcomes for patients. Despite the advances, unfortunately, many patients whose disease initially responds to the new therapeutics eventually relapse owing to treatment resistance.

Isatuximab-irfc is a CD38-targeted immunotherapeutic, like daratumumab, which was approved by the FDA in November 2015. CD38 is a protein found at high levels on the surface of myeloma cells. When isatuximab-irfc attaches to CD38, it has several effects on myeloma cells, one of which is to flag them for immune cells, which upon attaching to another part of isatuximab-irfc are triggered to destroy the myeloma cells. Isatuximab-irfc was approved for use in combination with pomalidomide and dexamethasone for treating patients with multiple myeloma that has relapsed or not responded to at least two other treatments, including lenalidomide and any one of the proteasome inhibitors. The approval was based on data from a phase III clinical trial that showed that adding isatuximab-irfc to pomalidomide and dexamethasone almost doubled the time before disease relapse (422).

Diffuse large B-cell lymphoma is the most common type of non-Hodgkin lymphoma diagnosed in the United States (see **Adding Precision to Treatment for Blood Cancers,** p. 87). Tafasitamab-cxix targets CD19, which is found on the surface of B cells, including diffuse large B-cell lymphoma cells. When tafasitamab-cxix attaches to CD19, it has several effects on diffuse large B-cell lymphoma cells, including flagging the cells for immune cells. Tafasitamab-cxix was approved for use in combination with lenalidomide for treating patients who have diffuse large B-cell lymphoma, not otherwise specified, that has relapsed or not responded to other treatment and who are not able to have an autologous stem cell transplant. The approval was based on data from a phase II clinical trial that showed that more than 50 percent of patients who received tafasitamab-cxix and lenalidomide had complete or partial tumor shrinkage, with the majority of these patients having complete tumor shrinkage (423). Additional follow-up and additional studies are needed to determine whether these immunotherapeutics also extend survival for patients.

SUPPORTING CANCER PATIENTS AND SURVIVORS

IN THIS SECTION YOU WILL LEARN:

- In the United States, there are more than 16.9 million people living with a history of cancer.
- Each person diagnosed with cancer faces a unique set of challenges, but one in four survivors reports a poor physical quality of life and one in 10 reports poor mental health–related quality of life.
- Several strategies, including adopting healthy behaviors and palliative care can improve quality of life and cancer-related outcomes.
- It is vital that we identify the optimal way to provide comprehensive, coordinated care to all survivors of cancer and ensure that this care improves cancer-related outcomes and health-related quality of life for all patients.

Research is driving advances in cancer detection, diagnosis, and treatment that 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 January 1, 2019, compared with just 3 million in 1971 (5)(424).

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.

Cancer survivorship encompasses three distinct phases: the time from diagnosis to the end of initial treatment, the transition from treatment to extended survival, and long-term survival. Each phase of cancer survivorship is accompanied by a unique set of challenges (see sidebar on **Life after a Cancer Diagnosis in the United States,** p. 112). Importantly, the issues facing each cancer survivor vary, depending on many factors, including gender, age at diagnosis, type of cancer diagnosed, general health at diagnosis, and type of treatment received.

One challenge facing patients and survivors with cancer that has emerged as increasingly important in recent years is financial hardship, or financial toxicity (425–427). Researchers studying financial hardship measure it in several ways: material financial hardship includes problems paying medical bills and depleting savings to pay medical bills; psychological financial hardship includes stress and worry about paying medical bills; and behavioral financial hardship includes delaying or forgoing cancer care because of cost. One recent study found that 25 percent of cancer survivors ages 18 to 64 reported material financial hardship and 34 percent reported psychological financial hardship (425). Another study showed that 42 percent of cancer survivors age 50 or older had depleted their entire life savings within two years of their cancer diagnosis (426).

Certain U.S. population groups are more likely to report financial hardship, including racial/ethnic minorities, individuals who have lower educational attainment, individuals who have lower family income, and individuals who lack health insurance (428–430). For example, in one study, cancer survivors who were African American were 23 percent more likely to report financial hardship than those who were white (429). Adolescents and young adults, as well as long-term survivors of childhood cancer, are also more likely to report financial hardship, particularly financial hardship caused by the indirect costs of lost productivity, such as days lost from work or disability days (431)(432).

Unfortunately, financial hardship is not the only challenge posed by cancer and cancer treatment that disproportionately affects certain segments of the U.S. population. There are disparities in many of the health complications related to cancer and cancer treatment that adversely affect the health and quality of life of patients and survivors with cancer, as well as disparities in receipt of care to overcome these complications (see sidebar on **Disparities in Health and Quality of Life after a Cancer Diagnosis,** p. 113).

LIFE AFTER A CANCER DIAGNOSIS IN THE UNITED STATES

When an individual is diagnosed with cancer, his or her life is changed irrevocably. Cancer survivors often face serious and persistent adverse outcomes, including physical, emotional, psychosocial, and financial challenges as a result of the cancer diagnosis and treatment. Many challenges experienced by cancer survivors begin during cancer treatment and continue in the long term, but others can appear months or even years later. These long-term and late effects include, but are not limited to:

- bone density loss (osteoporosis);
- cognitive impairment (trouble remembering, learning new things, concentrating, and/or making decisions that affect everyday life);
- diagnosis with a new type of cancer(s);
- distress, anxiety, and/or depression, which can interfere with a person's ability to cope effectively with cancer and its treatment;
- endocrine dysfunction, which is dysfunction of the collection of organs and glands that control body functions such as growth, sexual development, reproduction, sleep, hunger, and the way the body uses food;
- fatigue that is severe and often not relieved by rest;
- fear of cancer recurrence;
- hearing loss;
- heart damage (cardiotoxicity);
- infertility;
- insomnia;
- joint changes;
- lung (pulmonary) damage;
- lymphedema, which is swelling, most often in the arms or legs, that can cause pain and problems in functioning;
- metabolic syndrome, which occurs when an individual has three or more of the following health risk factors: excess body fat around the waist, high blood pressure, high triglycerides, impaired fasting glucose, and low HDL cholesterol;
- mouth changes;
- nerve problems (peripheral neuropathy);
- nutrition issues;
- pain;
- premature aging;
- recurrence (return) of original cancer; and
- sexual dysfunction.

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. For more information, see **http://survivorshipguidelines.org/**.

Adapted from (1)

IMPROVING QUALITY OF LIFE AND OUTCOMES ACROSS THE CONTINUUM OF CANCER CARE

For patients and survivors with cancer, quality of life is a multidimensional concept that goes beyond the person's cancer-related outcomes and considers their overall physical, mental, emotional, and social functioning (437). As more and more people are surviving longer after a cancer diagnosis, the issue of quality of life has become increasingly important across the continuum of cancer care (438).

In recent years, some of the changes in cancer treatment are helping to reduce the short-term, long-term, and late effects of treatment. This is improving quality of life for patients and survivors, allowing many of them to continue to live their lives, as **Congresswomen Lucy McBath** was able to do when she was treated for breast cancer (see p. 114). For example, molecularly targeted therapeutics more precisely target a patient's cancer cells compared with cytotoxic chemotherapeutics and therefore tend to cause fewer adverse effects. In addition, researchers are identifying ways to tailor surgery, radiotherapy, and cytotoxic chemotherapy to minimize their adverse effects without negatively affecting survival. The success of these approaches is highlighted by research showing that significantly fewer survivors of cancer diagnosed in childhood are experiencing and dying because of late effects of cancer treatment, such as a new cancer or heart disease, compared with three decades ago, and that this progress is expected to translate into further improvements in life expectancy for these individuals in the future (300)(439)(440).

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 cancer- and cancer treatment–related health complications that adversely affect health and quality of life after a cancer diagnosis. Examples of these disparities include:

20% LOWER	The proportion of Native American women who had breast reconstruction after a mastectomy to treat breast cancer was 20 percent lower than the proportion of white women who had this surgery, which has been shown to improve health-related quality of life for cancer survivors (433).
LESS LIKELY	African Americans who had advanced cancer were less likely to receive a palliative care consult compared with whites (434).
50% MORE LIKELY	Colorectal cancer survivors who had low socioeconomic status were 50 percent more likely to report clinically significant anxiety and depression compared with those who had high socioeconomic status (435).
23% MORE LIKELY	Cancer survivors who lived in rural areas were 23 percent more likely to report psychological distress compared with those in urban areas (436).

Despite advances in cancer treatment that are helping improve quality of life, individuals with a history of cancer consistently report worse general health and quality of life compared with people without such a history. For example, in one study, one in four survivors of cancer diagnosed in adulthood reported a poor physical quality of life and one in 10 reported a poor mental health-related quality of life compared with one in ten and one in 16 people without a history of cancer, respectively (441). Therefore, identifying new ways to improve quality of life throughout a patient's experience with cancer, beginning at diagnosis and continuing through treatment, follow-up, survivorship, and end-of-life care, is an area of intensive research investigation.

Improving quality of life is also important because research suggests that it is linked to cancer-related outcomes, including survivorship. In fact, several strategies, including some of those discussed below, such as outpatient specialty palliative care and exercise, have been shown to improve quality of life and survival (442)(443).

THE HONORABLE

LUCY MCBATH

AGE 60 | U.S. REPRESENTATIVE
FOR GEORGIA'S 6TH CONGRESSIONAL DISTRICT

Combatting Cancer and Disparities in Health Care

I'm a wife, mother, gun violence prevention advocate, and member of Congress. I am also a two-time breast cancer survivor, and I think it is important to share my experience fighting cancer and speak more about how important it is to support of medical research, which can help in the treatment of cancer and the development of a cure.

I was first diagnosed in 2002 during a routine mammogram. The doctors noticed calcifications on the images they took. They informed me that they found a sizeable lump in my left breast and then scheduled a biopsy. Miraculously, the mass they initially found disappeared, which was confirmed by additional X-rays and consultations with other physicians. My faith and the support of my family were essential in my fight against breast cancer. Several years later I was diagnosed with cancer again, and it was really difficult for my son, Jordan. Jordan was a teenager, and he felt helpless and afraid and didn't quite know how to deal with my diagnosis. I did everything I could to shield him from watching me go through treatment, because I knew that would be tough on him. Having survived cancer twice and having gone through all the treatments has really helped me understand how precious life is—it really is a gift.

During the time between my diagnoses, new medicines and more effective treatments were made available, and I've seen firsthand the importance of federal investment in medical research. During my second cancer fight, I would go to work in the morning, drive to the hospital to get my treatment, and then would go back to work after it was over. Many people with cancer can now live fairly normal lives outside of their treatment, and that is so important because it allows people to have a sense of normalcy. They can continue to be with their friends and loved ones and just focus on getting better.

Had it not been for much of this valuable medical research and the innovative and new treatments born out of the research, I'm not sure I would be here today. As a member of Congress, my focus has been on making sure that researchers have access to the funds they need to create new treatments and discover new cures. I have supported increases in funding to the National Institutes of Health (NIH) and Department of Defense's Congressionally Directed Medical Research Programs that support cancer research. I have also supported increased public health measures, such as screening for prostate and breast cancer. I owe my life to the scientists, physicians, and medical professionals that work every single day to help people like me. They are truly saving lives.

Unfortunately, there are many health inequities that communities of color face, and this has played an integral role in the poor outcomes we are seeing today. I believe that we must invest in those communities that are suffering these disparities. If we want to decrease the incidences of cancer, there are a host of social ills we must identify and address. I have introduced bills that would use federal agencies to address the social determinants of health in health-impoverished communities. I have worked and will continue to work very hard to identify and break down the barriers that prevent people from accessing the health care they need to have healthier and longer lives.

Groups like the American Association for Cancer Research (AACR), and other advocacy groups, play an important role in communicating the needs of the cancer research community to Congress. They have done an excellent job in explaining how far NIH dollars go into the community and how important federally funded research is to innovation in medical research. The AACR has also been successful in putting a human face to cancer. All too often policy comes down to some stats on a sheet, and while understanding the scope of the problem is important, there is nothing more powerful than having that face to face interaction with advocates. Hearing their struggles and passion helps makes us better policy makers.

In the meantime, my health is great, and I feel really good, and I am so thankful. Like most cancer survivors, I am concerned about cancer recurrence. Like many cancer survivors, when I go for my follow-up exams, there is always a bit of hesitation and anxiousness. But I feel so lucky to be doing the work I am doing, and I try to live my life every day the best I can because there is still so much work to do.

I have worked and will continue to work very hard to identify and break down the barriers that prevent people from accessing the health care they need to have healthier and longer lives.

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.

Adapted from (30)

Promoting Healthy Behaviors

Evidence is emerging that modifying behaviors to eliminate or avoid many of the lifestyle-related factors that increase a person's risk of developing cancer, such as cigarette smoking, physical inactivity, unhealthy diet, and alcohol consumption, can improve outcomes and quality of life for cancer patients and survivors (444) (445) (see **Preventing Cancer: Identifying Risk Factors,** p. 37).

In addition to being the leading preventable cause of cancer, cigarette smoking can increase risk of death from cancer, risk of cancer recurrence, risk for developing a second cancer, risk of treatment-related toxicity, and risk of a poorer response to treatment (446). Fortunately, patients and survivors with cancer who are current smokers can improve their prognosis by quitting smoking. Quitting smoking can also reduce fear of cancer recurrence, which is an adverse long-term and late effect of cancer and cancer treatment (447). Despite this knowledge, 9 percent of survivors continue to smoke years after a cancer diagnosis and young adults ages 18 to 39 who have a history of cancer are more than 50 percent more likely to have used e-cigarettes compared with their peers who have no history of cancer (448). Therefore, more research is needed to develop optimal strategies to provide patients with cancer who smoke with the best chance of quitting smoking, with recent studies suggesting that digital technology and app-based approaches may provide new avenues for promoting smoking cessation (449–451).

Just as exercising regularly can reduce the risk of developing certain types of cancer, it can also reduce recurrence and mortality for survivors of several types of cancer, including breast cancer, childhood cancer, colorectal cancer, and prostate cancer (443) (452-454). In addition, exercise can improve overall quality of life for patients and survivors who are undergoing treatment for cancer and for those who have completed treatment (454–456). More specifically, exercise during and after treatment is completed has been shown to alleviate many of the adverse long-term and late effects of cancer and cancer treatments, including anxiety, depression, cognitive impairment, fatigue, lymphedema, pain, peripheral neuropathy, and poor sleep quality, and to improve heart and lung function (457–463). The beneficial effect of exercise on heart function among patients with cancer is particularly important because research shows that many patients with cancer are at increased risk of death from cardiovascular disease, in particular, those who have bladder cancer, breast cancer, or prostate cancer (463)(464).

Eating a diet rich in vegetables, fruits, and whole grains, or a diet high in fiber, reduces a person's risk of developing or dying from some types of cancer, in particular, colorectal cancer, and can improve quality of life after a cancer diagnosis (465) (466) (445). Conversely, consuming alcohol increases risk of death from prostate cancer after a prostate cancer diagnosis, and consuming three to four alcoholic drinks a week increases risk of recurrence among patients and survivors with breast cancer (467) (468). Despite this knowledge, more than half of a group of 34,080 survivors of various types of cancer reported that they currently drank alcohol regularly, with 21 percent of these drinkers saying that they engaged in binge drinking (469).

The growing body of evidence that modifying lifestyle-related behaviors, such as physical inactivity, unhealthy diet, and alcohol consumption can improve outcomes and quality of life for cancer patients and survivors has led experts to recommend that cancer patients and survivors achieve and maintain a healthy body weight, participate in regular physical activity, and eat a diet rich in vegetables, fruits, and whole grains (178).

Palliative Care

Palliative care is one approach that is being increasingly used to optimize the quality of life for patients and survivors with cancer, as well as their families and caregivers (see sidebar on **What Is Palliative Care?** p. 116). Palliative care 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. The goal is not to treat the cancer but to provide an extra layer of care that prevents or treats the symptoms and adverse effects of the disease and its treatment, as well as addresses the psychological, social, and spiritual challenges that accompany a cancer diagnosis.

Recent research shows that integrating palliative care during the early stages of cancer care can significantly improve quality of life and survival, and lower hospital costs (442) (470) (471). Despite this, the only growth in palliative care infrastructure that has occurred in the past decade is in outpatient palliative care clinics at NCI-designated cancer centers. There has been no increase in inpatient consultation teams, palliative care units, and institution-operated hospices at either NCI-designated cancer centers or at non–NCI-designated cancer centers, and there has been no increase in outpatient palliative care clinics at non–NCI-designated cancer centers (472).

It is imperative that we increase awareness of the important role that palliative care can play across the continuum of clinical cancer care because many patients do not receive palliative care and many patients and caregivers do not even know what palliative care is (473) (474). One study found that patients with cancer were more likely to express a preference for early outpatient palliative care after being provided a web-based, plain-language and graphical summary about palliative care as well as the information about the results of a clinical trial which showed that palliative cancer care improved physical quality of life, depression, and survival for patients with metastatic lung cancer (475). It will be important to determine whether such programs benefit all segments of the U.S. population because it has been reported that there are disparities in the use of palliative care among patients with cancer (434).

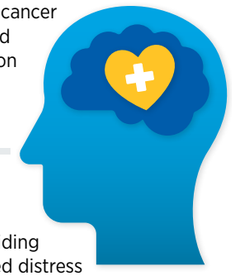
Psycho-oncology

Psycho-oncology is a field of research and branch of medicine that encompasses the work of researchers and health care providers committed to developing new approaches to addressing the behavioral, emotional, psychological, and social challenges posed by cancer (see sidebar on **Helping Patients with Cancer through Psycho-oncology Research,** p. 117). Addressing these challenges, which include treatment-related cognitive impairment, fear of cancer recurrence, anxiety, depression, stress, posttraumatic stress disorder, and feelings of despair, is important not just for improving quality of life, but also for improving outcomes because challenges such as depression, anxiety, and low levels of social support are often associated with decreased adherence to cancer treatment and/or decreased survival (476–478). Given the benefits of psycho-oncology, it is vital that all patients with cancer for whom this intervention is appropriate receive this care.

HELPING PATIENTS WITH CANCER THROUGH PSYCHO-ONCOLOGY RESEARCH

Health care practitioners working in the field of psycho-oncology, including psychiatrists, psychologists, nurses, and social workers, are dedicated to addressing the behavioral, emotional, psychological, and social challenges faced by patients and survivors with cancer. Approaches to helping these individuals tested in recent psycho-oncology clinical trials include:

Having a form of cognitive behavioral therapy called acceptance and commitment therapy, or ACT, comprising six group sessions lasting 2 hours, reduced fear of cancer recurrence, anxiety, and symptoms of depression among patients with breast cancer (479).



Attending a 1-week outdoor adventure therapy program providing peer support decreased distress symptoms and increased self-efficacy and social support among young adults ages 18 to 40 who have cancer (480).

DELIVERING CARE TO CANCER SURVIVORS

As an increasing number of people are surviving longer after a cancer diagnosis, it has become increasingly clear that the transition from initial cancer treatment to follow-up, long-term survivorship care can be complex.

Coordinating Care

Most survivors of cancer have poorer health and quality of life than other individuals of a similar age who have no history of cancer. They are also at increased risk for long-term morbidity and premature mortality due to their cancer diagnosis and treatment. Therefore, survivors have complex health care needs that are best met by a wide range of health care professionals (481).

Emerging evidence suggests that survivors of cancer receive the highest level of care if their care is well coordinated, either by an oncologist and primary care physician, by multiple specialists, or by an oncogeneralist—a primary care physician with specific expertise in caring for patients and survivors with cancer (438) (481–483). However, we need to identify the optimal way to provide comprehensive, coordinated care to all survivors of cancer and ensure that it benefits patients by improving cancer-related outcomes and health-related quality of life (481)(484).

The Important Role of Caregivers

Caregivers provide an extension to a cancer survivor's health care team. They play a vital role throughout a patient's experience with cancer, from diagnosis through long-term survivorship. The population of caregivers is growing proportionally with the number of cancer survivors. One recent study of caregiving in 18 states in the United States led researchers to estimate that there are 1.1 million family caregivers of adults with cancer living in these states and that more than one in five of these people were caregiving for more than 20 hours per week (485).

It is important to note that caregivers are at risk for poor health outcomes, in particular poor mental health outcomes. Those who are caregiving for longer hours experience worse outcomes (485). Research such as this is bringing increasing awareness to the need for new strategies to optimize and tailor support for caregivers.

LOOKING TO THE FUTURE

IN THIS SECTION YOU WILL LEARN:

- Cutting-edge technologies that fuel the full spectrum of cancer science from bench to bedside will accelerate the pace at which we increase our understanding of cancer biology while transforming the future of clinical practice.
- As researchers accumulate large quantities of patient data, artificial intelligence approaches such as machine learning programs have the potential to help us analyze these vast amounts of health care information to derive meaningful insights we previously could not have realized.
- Liquid biopsies have the potential to transform early detection, diagnosis, and treatment of cancer in the future.
- Our scientific understanding of the immune system and how it interacts with cancer cells is rapidly increasing, and numerous clinical trials are underway that are testing many novel immunotherapeutics and new ways to use those immunotherapeutics that we already have.

This is an incredibly exciting time for cancer science and medicine. Increasing public awareness of cancer prevention and early detection coupled with the development and approval of a range of novel anticancer therapeutics has led to dramatic reductions in overall cancer death rates for all Americans. Continued advances in the fields of cancer genomics and immunology are driving remarkable progress in the newest treatments in cancer care—molecularly targeted therapy and immunotherapy—which are benefiting many patients with a range of cancer types. The pace of progress in these research areas is expected to accelerate in the coming years for the benefit of patients with cancer.

Despite these advances, cancer continues to be an enormous public health challenge in the United States and worldwide. In fact, it is predicted that more than 606,520 people in the United States will die from some type of cancer in 2020. Furthermore, the medical research community has been inundated with numerous challenges due to the recent COVID-19 pandemic which has dampened the ongoing momentum in cancer research. However, many researchers, including **AACR President, 2020–2021, Antoni Ribas, MD, PhD,** are extremely hopeful about the future because they are confident that through collaborative and innovative research we will be able to overcome the public health crisis caused by COVID-19 while we continue to power more advances against cancer (see p. 120). The new wave of scientific and technological innovations discussed in this chapter has the potential to transform patient care in the years to come.

ARTIFICIAL INTELLIGENCE

According to the 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 and pathological slides, cancer and patient genome profiles, and electronic health records to clinical outcomes, AI can analyze this information to derive meaningful insights that we previously could not have realized (486). 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. Some recent advances in the field are described below.

AI in Cancer Imaging

One of the most exciting areas of cancer research where AI is already showing great promise is cancer imaging. Analysis of images from normal tissue, precancerous lesions, or cancers derived from various means including clinical photographs (from endoscopy, colonoscopy, etc.), radiological images (from mammography, lung CT, etc.), or histological images (from tumor pathology), is a critical step in cancer detection and diagnosis. Traditionally, interpretation of these images is

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Anticipating More Progress for Patients with Cancer through Scientific and Technological Innovation

During the 20 years that I have been a physician-scientist, I have seen unparalleled advances in cancer science and medicine, and I am excited for the future. In the next 10 years, I expect that scientific discoveries will ignite another revolution in cancer treatment and further improve outcomes for patients with cancer.

When I was completing my medical training in the late 1990s, most patients with cancer were treated with surgery, radiotherapy, and/or chemotherapy. These treatments cured some patients, but most patients with metastatic cancer did not have curative treatment options. The landscape of cancer care has been revolutionized by knowledge generated through scientific and technological innovation. Growing knowledge about genetic mutations that yield dysregulated proteins that drive cancer is being applied to the development of therapeutics that specifically target the dysregulated proteins. Deepening knowledge about interactions between cancers and the immune system has been harnessed to develop immunotherapeutics that power immune cells to attack cancers.

Since I began treating melanoma, I have seen firsthand the significant benefit that molecularly targeted therapy and immunotherapy have had for patients. Twenty years ago, only about one in 20 of the patients with advanced melanoma responded to the treatments we were using at that time—chemotherapy and cytokine therapy. Now, about half of the patients with advanced melanoma are doing well in the long term thanks to targeted therapeutics that target BRAF and MEK and immune checkpoint inhibitors that stimulate the immune response to attack the melanoma.

Molecularly targeted therapy and immunotherapy are just two examples of how the increased scientific understanding of cancer biology that has been gained in the past 5 to 10 years has led to significant advances for patients.

As we move forward, the paradigm of applying scientific and technological innovation to transform cancer prevention, detection, diagnosis, and treatment will continue apace. We are already beginning to investigate the potential of a new technology called liquid biopsy to detect cancer early in development, including those types of cancer that are currently hard to detect such as ovarian cancer. There is still a way to go, but I foresee that in a few years, this technology will allow us to draw a person's blood, analyze it for molecular signatures of cancer, and identify who is developing a cancer before it is detectable with a CT scan. This will allow cancer to be detected at an early stage, when it is more likely that it can be treated successfully.

Another area in which scientific and technological innovation are intersecting to drive progress is in the development of the next generation of genetically modified T-cell therapies (see **Increasing the Cancer-killing Capacity of the Immune System,** p. 108). CAR and TCR T-cell therapies involve harvesting immune cells called T cells from a patient's blood, genetically modifying the T cells to endow them with an artificial receptor that redirects them to target and kill cancer cells, and then expanding the number of T cells before infusing them back into the patient. Researchers are now combining our knowledge of T cells and cancer biology with new technologies such as CRISPR gene editing to develop next-generation cell therapies that have longer-lasting, more robust anticancer effects.

In 2020, the cancer research community, like every other community around the world, has had to face a new challenge, the COVID-19 [Coronavirus Disease 2019] pandemic. This challenge is 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.

In addition, the COVID-19 pandemic has highlighted stark inequities in health care for racial and ethnic minorities and other underserved populations. The AACR [American Association for Cancer Research] has long been a leader in the field of cancer health disparities research, and we are extending these efforts to include all health disparities, including disparities in COVID-19.

The COVID-19 pandemic has stifled progress against cancer and is predicted to exacerbate cancer health disparities. Therefore, it is vital that Congress continue to make medical research a national priority. Federal investment is urgently needed if we are to get this pandemic under control and return to our mission of preventing and curing all types of cancer.

In the next 10 years, I expect that scientific discoveries will ignite another revolution in cancer treatment and further improve outcomes for patients with cancer.

carried out by expert physicians through a process that is both laborious and time consuming. Several recent studies indicate that image analysis using AI has the potential to streamline processes that are necessary for accurate interpretation of images from numerous sources routinely used in cancer medicine. Notably, these reports highlight that AI is capable of spotting cancers with similar accuracy to, and in cases, higher accuracy than human experts, which allows for faster clinical decision-making for those with life-threatening cancers. Thereby, AI can also expand access to quality care in underserved regions where qualified clinical staff are lacking or scarce by taking over some of the diagnostic duties typically allocated to expert health care professionals.

Analyzing Clinical Photographs

The utility of AI in detecting cancerous polyps by analyzing digital photographs of the GI tract taken during routine endoscopy or colonoscopy procedures is an area of extensive investigation and in fact shows great promise in the detection of both gastric and colorectal cancers (487) (488). Furthermore, according to a recent report, a machine learning approach outperformed human experts in detecting precancerous changes in cervical images obtained from volunteers who took part in a cancer screening study conducted in Costa Rica over two decades ago (489). Ongoing research is testing whether such an approach may be utilized to detect cervical cancers using high-quality photos of the cervix taken by smartphones during a routine pelvic exam. Such low-cost, mobile methods could provide a valuable new tool to help reduce the burden of cervical cancer especially among underserved populations both in the U.S. and around the globe (490).

Investigating Radiology and Pathology Images

Further examples of the use of AI in cancer imaging include radiological imaging analysis and pathology testing results determination, both of which are critical in diagnosing cancer. Traditionally, the former involves a radiologist scanning images by visually searching for signs of cancer while pathology testing involves a pathologist viewing a slide on which there is a slice of the abnormal tissue under a conventional light microscope to determine the presence of cancerous cells. Current methods of analyzing scans and slides are time consuming and can sometimes miss signs of cancer (false negative) or detect cancers that turn out to be imaging artifacts (false positive).

Emerging data highlight that AI can play a critical role in increasing the efficiency and accuracy of both radiology and pathology image analyses. For instance, recent studies have demonstrated that AI tools can better detect breast or lung cancers from mammograms or CT scans, respectively, compared with radiologists, resulting in fewer cases of false positives and false negatives (278) (491). AI systems have also been shown to detect and characterize abnormality in tumors from prostate cancer biopsies at an efficiency that is comparable to that of pathologists (492). Yet another remarkable use of AI, as documented in a recent report, is to rapidly provide surgeons with accurate, real-time information about the type of brain tumor a patient has while the patient is being operated on. The researchers found that AI could analyze pathology images from a biopsy sample obtained during surgery to accurately diagnose the type of brain tumor in fewer than 3 minutes, a process that traditionally takes about 40 minutes (493). The approach was also able to accurately distinguish tumor from surrounding healthy tissue, which can refine surgery and may result in major improvements in long-term patient outcomes. In addition to its role in cancer diagnosis, AI methods may help researchers accurately predict the presence of certain biomarkers (e.g., genetic mutations or proteins) in tumors by analyzing pathology images (494) (495). Such AI-based approaches could potentially be faster and less expensive compared with traditional techniques of biomarker detection, may allow for simultaneous profiling of multiple biomarkers in cancer tissues, and could transform the future of precision medicine.

AI in Drug Development

Researchers are harnessing the power of AI in many ways to accelerate cancer drug discovery (496). While some efforts are aimed toward making basic research investigations more effective, others have the goal of streamlining clinical trials to make them more efficient. In fact, the use of AI can augment each step of the drug development process (see sidebar on **Therapeutic Development,** p. 69). 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, e.g., 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 (497). In this regard, one initiative currently underway is utilizing AI to identify novel ways to inhibit the activity of an altered KRAS protein, one of the most frequent alterations found in cancers (498).

In clinical research, AI platforms including machine learning can accelerate cancer drug discovery by using biomarkers to accurately select patient populations in which to test new therapeutics while preventing serious adverse events by identifying high-risk individuals prior to patient enrollment. Furthermore, AI has the potential to improve clinical trial efficiency by incorporating information from historical control arms or real-world data, predicting effective combinations of drug targets that may improve patient outcomes. An area of urgent research focus is the diversification of datasets used to train AI platforms from primarily Caucasian populations to include racial and ethnic minorities and other underserved groups.

AI in Patient Care

Beyond its role in rapidly advancing the entire continuum of cancer research, it is anticipated that AI may also play a crucial role in patient care in the near future. AI has the potential to aid in clinical decision-making such as in deciding on the best treatment options for patients or in identifying responses to therapy, among other applications. As an example, in a recent study, researchers utilized data from computed tomography scans from patients with lung cancer to create an AI model that was able to analyze patterns within the tomography scans to predict how patients may respond to chemotherapy, targeted therapy, or immunotherapy (499). This model offers a promising approach to guiding clinical decisions and forecasting patient outcomes.

Another area in patient care where AI may play a pivotal role is in addressing the challenges of treatment resistance (see sidebar on **The Challenge of Treatment Resistance,** p 86). Treatment resistance arises when certain cancer cells deploy necessary mechanisms to overcome the cancer-killing effects of the treatment, continue to multiply, and eventually outnumber the drug-sensitive cells to repopulate a tumor. Some researchers now believe that using high doses of therapeutics to eliminate the maximum number of cancer cells may accelerate the emergence of resistant cell populations (496)(500). Therefore, an area of extensive investigation in AI is the application of mathematical models to identify optimal dosing regimens of therapeutics that will maintain a persistent population of drug-sensitive cancer cells in a tumor (500)(501). Researchers hypothesize that maintaining a threshold level of drug-sensitive cells that compete for growth with resistant populations will prevent or slow the multiplication of resistant cell populations.

Across the continuum of cancer care there is growing interest in utilizing AI coupled with patient data and treatment guidelines to guide cancer management, although the full potential of such approaches remains to be determined. For instance, in a recent study, AI was able to utilize data from electronic health records to identify patients with cancer who are at high risk of short-term mortality, allowing health care providers to engage in more timely conversations regarding patients' goals and values (502).

Collectively, these reports emphasize the incredible potential of AI in the future of clinical cancer care. However, as mentioned above, an area where researchers must pay close attention is the inclusion of diverse datasets that are representative of the U.S. population during the development of AI platforms. Lack of diversity in the data that are used to train AI or machine learning systems may incorporate racial/ethnic or other biases within AI applications and limit their generalizability for all patients who must benefit from these state-of-the-art technologies (503)(504).

MINIMALLY INVASIVE TESTING USING LIQUID BIOPSIES

A biopsy is the removal of cells or tissues from a patient for testing to help physicians diagnose a condition such as cancer or monitor how it changes in response to treatment. Traditionally, biopsies are invasive procedures. However, research has shown that during cancer development and treatment, tumors routinely shed detectable cells, lipid encapsulated sacs called exosomes, and free DNA into a patient's blood or cerebrospinal fluid. Recent studies have also shown that it is possible to use a blood or another biofluid sample, or "liquid biopsy," rather than a traditional tissue biopsy, to obtain material that can be analyzed to provide valuable information such as the molecular alterations associated with a patient's cancer (505). Liquid biopsies, therefore, provide a less invasive means to detect or track the status of cancer. There is much excitement in the cancer field that, as opposed to traditional biopsies which only provide a snapshot of the tumor characteristics at one specific timepoint, liquid biopsy approaches may generate a more complete picture of an individual's cancer by allowing for the monitoring of disease progression and its response to treatments in real time.

Ongoing research is evaluating multiple liquid biopsy approaches. Some liquid biopsy platforms analyze blood samples to identify specific genetic or epigenetic alterations in the DNA that are associated with certain cancer types, while others look more broadly at the patterns of fragmentation of the shredded cell-free DNA in the blood, and yet others aim to detect tumor-associated proteins in the blood (506–509). Early clinical data indicate that liquid biopsies have the potential to transform early detection, interception, diagnosis, treatment, and surveillance of cancer by identifying markers of disease, therapeutic response, resistance, and recurrence (see **Figure 20,** p. 124) (510–512). Selected examples of recent research examining the role of liquid biopsies across the spectrum of cancer research are presented here.

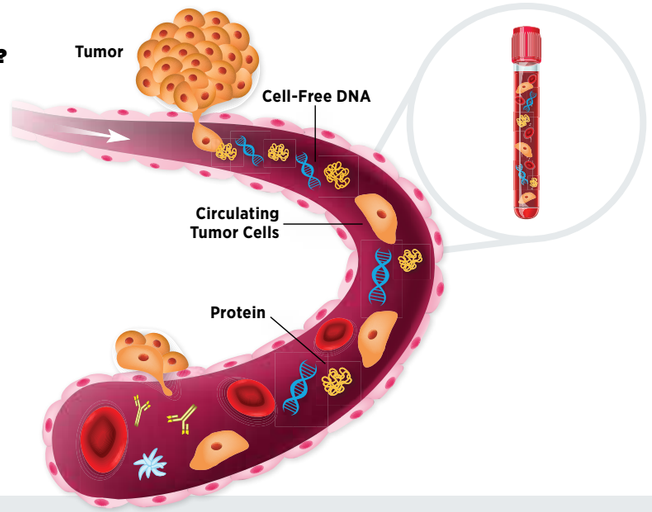
Detecting Cancers Early

In a recent study, researchers were able to utilize a blood test combined with imaging techniques to detect cancers in women without any prior history or symptom (280). The test identified breast, lung, and colorectal cancers for which there are recommended screening tests, but also seven additional cancer types such as ovarian, uterine, and kidney cancer for which there are no screening tests available at the current time. Notably, some of the cancers were detected at an early stage, when interventions are most likely to be effective. A second liquid biopsy platform utilized innovative DNA sequencing methods to analyze specific patterns in the circulating DNA to detect more

FIGURE 20 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?**



Liquid biopsy refers to the collection and analysis of blood or other biofluids. In cancer science and medicine, it primarily involves the capture and analysis of cells, lipid-encapsulated sacs called exosomes, or free DNA shed by tumors. As a result, a blood sample, rather than a biopsy of the tumor tissue itself, could be used to analyze genomic alterations in a patient's cancer. Liquid biopsies have the potential to be safe and less invasive for the patient, more likely to result in patient compliance, and may be better representative of tumor heterogeneity than a typical biopsy. Currently, liquid biopsies are used in the clinic to detect mutations in cancers that are targetable by therapeutics. Ongoing research is assessing the value of liquid biopsies in detecting cancers early, evaluating response to treatment, detecting treatment resistance and evaluating tumor heterogeneity, and monitoring minimal residual disease, among other uses.

than 50 different types of cancer (281). An added benefit of this platform was that it was able to identify the tissues in which the cancer originated. While these reports are very promising, additional research is needed to determine whether cancer detection using liquid biopsies can ultimately reduce the number of deaths from cancer, before such tests can be introduced to the clinic. Furthermore, potential harms of detecting slow-growing cancers that would have never caused serious harms during an individual's lifetime, a phenomenon known as overdiagnosis, and of unnecessary invasive interventions known as overtreatment, need to be weighed against potential benefits.

Making Treatment Decisions

While molecularly targeted therapies have transformed the landscape of cancer treatment for many diseases such as lung or breast cancer, it is often difficult to use traditional biopsies to test for all genetic alterations in the cancer that may be therapeutically targetable. Underlying reasons may vary ranging from lack of adequate biospecimen or lack of quality biospecimen, to compliance and bioethical issues. In this regard liquid biopsies provide a great alternative. They are potentially safer and less invasive for the patient and may better represent the tumor heterogeneity than a typical biopsy. Therefore, one of the biggest appeals and the only FDA-approved use of this technology is as a companion diagnostic in identifying cancer-causing mutations to make treatment decisions for patients. Thus far, two liquid biopsy companion diagnostic tests have been approved by the FDA. In June 2016, the FDA approved the first for identifying whether a patient with metastatic NSCLC is eligible for treatment with the EGFR-targeted therapeutic erlotinib. In May 2019, the FDA approved the second liquid biopsy companion diagnostic test which detects PIK3CA mutations in individuals with HER2-negative, advanced or metastatic breast cancer. Ongoing research is underway to develop and validate numerous new liquid biopsy platforms that can simultaneously detect multiple targetable genetic alterations using blood or other biofluid samples from patients with cancer (510). It remains to be determined whether such tests can detect therapeutically targetable mutations with the same accuracy as traditional biopsies and whether treatments based on liquid biopsy-derived information can result in comparable long-term outcomes for patients with cancer.

Predicting Cancer Resistance and Recurrence

Liquid biopsies may also provide researchers with important clues as to whether a patient's cancer has the potential to spread, grow resistant to treatments, or relapse. For instance, ctDNA analysis in patients with gastric cancer expressing the protein HER2 and treated with the HER2-targeted therapeutic trastuzumab allowed researchers to gain novel insights into the genetic alterations that contribute to resistance to the targeted therapeutic (511). According to another recent report, the prevalence of circulating tumor cells and the presence of certain genetic alterations within those cells detected during surgery of early-stage NSCLCs could predict the recurrence of metastatic cancer (513). Similar data have emerged in colon cancer where the detection of circulating tumor DNA after surgery or after adjuvant chemotherapy was associated with excess risk for disease recurrence during a 3-year follow-up (514). In addition, ongoing research is underway to evaluate the clinical utility of circulating tumor DNA detection in determining the risk of recurrence of a particularly intractable form of breast cancer known as triple-negative breast cancer (515).

NEW WAVE OF INNOVATIONS IN CANCER IMMUNOTHERAPY

Cancer immunology and immunotherapy are some of the most exciting areas of cancer research. In the past decade, immunotherapeutics have revolutionized the landscape of cancer treatment. As described in **Treatment with Immunotherapy** (see p. 97), these therapeutics work in many ways (see sidebar on **How Immunotherapeutics Work,** p. 100). However, thus far, immunotherapeutics have been successful in treating only a small fraction of patients with cancer. Furthermore, many patients who respond initially may develop resistance after a period of time. Researchers are working diligently to increase the number of patients who benefit from these groundbreaking treatments. Novel avenues that are being pursued include identifying ways to select the right patients who have a higher probability of responding to existing immunotherapies as well as designing new immunotherapeutics that may benefit additional patient populations. While most immunotherapeutics approved by the FDA to date have focused on the anticancer effects of a type of immune cells called T cells, researchers are now harnessing the power of many additional types of immune cells with distinct functions to attack and kill cancer (see sidebar on **Key Players in the Immune System,** p. 126). In the following sections we describe some of the exciting new approaches that are being investigated.

BIOMARKERS

Biomarkers are cellular and molecular (including genetic and epigenetic) characteristics by which normal and/or abnormal processes can be recognized and/or monitored. They are measurable in biological materials such as tissues, cells, and/or bodily fluids.

Expanding the Scope of Checkpoint Inhibitors

Among the most promising anticancer therapeutics that have emerged in the last decade are checkpoint inhibitors. These molecules work by releasing certain brakes on the natural cancer-fighting power of the immune system (see **Releasing the Brakes on the Immune System,** p. 97) and have transformed the care of many aggressive cancers including melanoma and NSCLC. Unfortunately, only a fraction of patients respond to checkpoint inhibitors, and many who do respond initially develop resistance after a while. Identifying the right patients who are most likely to have durable responses is key to guiding treatment decisions and is an area of active research. In order to select the right patients, it is important to understand the cellular and molecular features of the tumors that influence response to checkpoint inhibitors. Many approaches are being pursued to characterize these features including state-of-the-art imaging techniques and quantitation of measurable tumor characteristics referred to as biomarkers which can predict treatment outcomes.

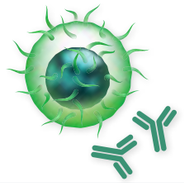
Advanced Imaging to Guide Immunotherapy

Immune cells called T cells are naturally capable of destroying cancer cells and are also the targets of checkpoint inhibitors which release certain brakes on T cells to mobilize them to kill cancer cells. Imaging T-cell localization in a patient's tumor may provide information about how the tumor is responding to checkpoint inhibitors. Positron

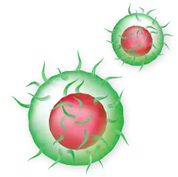
KEY PLAYERS IN THE IMMUNE SYSTEM

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

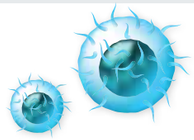
B cells make antibodies that help the immune system function. Some remain as memory B cells to make the same antibody again later, if it is needed



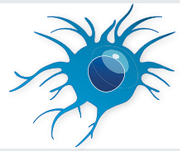
CD4+ T cells help manage the immune response. Some remain as memory T cells to fight again later.



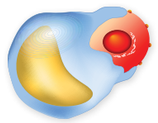
CD8+ T cells kill infected, damaged, and cancer cells. Some remain as memory T cells to fight again later.



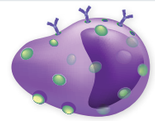
Dendritic cells educate T cells about what kinds of cells they should and should not attack.



Macrophages eat foreign materials.

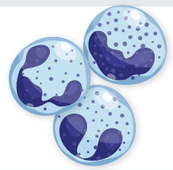


Mast cells release chemicals against pathogens and stimulate the immune system.



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

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



Adapted from (57)

emission tomography (PET) offers an attractive approach for imaging tumors. In a traditional PET scan the whole body is imaged by intravenously administering a radioactive molecule such as 18F-fluorodeoxyglucose to a patient, which helps to visualize multiple tumors at once. To visualize the immune cells, researchers have developed an alternative method called immuno-PET, which uses radiolabeled antibodies that bind to specific proteins on the T-cell surface providing information about their localization (516). While conventional antibodies are large molecules and only achieve low levels of penetration in the tumor tissue, researchers have devised smaller molecules called "nanobodies," which contain fragments of an antibody and could potentially be more easily taken up by the tumor tissue (517). Using nanobodies that bind to a cell-surface protein CD8, which is found on cancer-killing T cells, researchers were able to visualize the trafficking of T cells into the tumor microenvironment. In animal models of colorectal cancer it was shown that tumors that respond to checkpoint inhibitors have a higher degree of CD8-expressing T cell infiltration throughout their core (517). Ongoing research is underway to determine whether this technique could be used in the clinic to help predict which patients will respond to immunotherapeutic regimens.

Using Biomarkers to Predict Responses to Immune Checkpoint Inhibitors

Cellular or molecular characteristics of tumors, referred to as biomarkers, can sometimes help researchers to predict clinical outcomes and to stratify patients as likely responders or nonresponders to therapeutics, including immune checkpoint inhibitors. Currently, three biomarkers are approved by the FDA to predict response to checkpoint inhibitors: the amount of checkpoint protein PD-L1 in the tumor tissue, and two different genetic characteristics of tumors—mismatch repair deficiency/microsatellite instability, and high tumor mutational burden. However, there has only been modest success in using these biomarkers to predict response, and current methods to measure them can be invasive, underscoring the need for more accurate and noninvasive biomarkers. For instance, determination of PD-L1 levels correlates only moderately with patient survival and response to anti-PD-L1 checkpoint inhibitor treatment. Heterogeneity of PD-L1 expression within and across tumors in a patient might limit the predictive value of the current methods that are used to quantify PD-L1 levels using tissue pathology. Notably, according to recent reports, tumor PD-L1 and PD-1 expression in patients with NSCLC can be quantified noninvasively through PET scanning using radiolabeled molecules that bind to PD1 or PD-L1 (518)(519). The researchers found that a lack of response to checkpoint blockade corresponded with low PD-L1 expression, indicating a prognostic utility for these advanced PET techniques. Noninvasive imaging methods such as these can evaluate multiple tumors simultaneously, as opposed to traditional methods using a tissue biopsy, and may address the issues of heterogeneity. Combination with key additional clinical information such as tumor genetics, as well as other novel biomarkers relevant to checkpoint inhibition, for example, genetic information derived from abnormal immune-related tissue formations called tertiary lymphoid structures found in cancer (520) (521), may help improve outcomes for patients.

Combining Therapeutics to Address Treatment Resistance

In order to overcome treatment resistance to immune-checkpoint inhibitors, researchers are currently investigating the underlying mechanisms of such resistance. The goal is to identify potential approaches to bypassing or overcoming the cellular and molecular pathways that lead to treatment resistance. In this regard, one approach that is currently being evaluated is combining checkpoint inhibitors with a range of therapeutic modalities, including molecularly targeted therapeutics, a separate checkpoint inhibitor, as well as other types of immunotherapeutics. For instance, a recent preclinical study identified the underlying mechanisms by which mutations in three proteins JAK1, JAK2, and beta-2-microglobulin (B2M), all of which regulate key immune-activating pathways, render patients with melanoma resistant to treatment with immune checkpoint inhibitors (522). The researchers proposed that a combination therapy using a molecule, bempegaldesleukin (BEMPEG), which can reverse the effect of B2M mutation, may be able to restore responses to checkpoint inhibitors. Notably, an early clinical trial that examined a combination of BEMPEG with the anti-PD-1 checkpoint inhibitor nivolumab in patients with various solid tumors, including melanoma, found that the combination led to encouraging clinical responses that are worth further exploration (523).

Targeting Novel Immune Checkpoints

Thus far the FDA has approved seven immune checkpoint inhibitors that inhibit proteins PD-1, PD-L1, and CTLA-4, for the treatment of numerous cancer types. However, given that many patients do not respond to the currently approved inhibitors and many others develop resistance after initial response, the identification of new checkpoint pathways to target therapeutically is a key area of immunotherapy research. Two checkpoint proteins that are both expressed on T-cell surface and are currently being tested as potential targets for anticancer therapy are the poliovirus receptor-related immunoglobulin (PVRIG) and T cell immunoreceptor with Ig and ITIM domains (TIGIT). Similar to the interaction of PD-1 with PD-L1, when checkpoint proteins PVRIG or TIGIT on T cells interact with their counterparts which are often expressed on the surface of cancer cells, T cells are "turned off" and the cancer cell is able to evade the immune response. The clinical impact of inhibiting PVRIG and TIGIT, alone or in combination with PD-1/PD-L1 inhibition is currently being evaluated in the clinic (524) (525). Targeting a third immune checkpoint protein, OX40, is another ongoing area of therapeutic investigation in immunotherapy. In contrast to the PD-1 and PD-L1 interaction, the interaction between OX40 protein on T cells and its binding partner on tumors enhances immune system function. In fact, there is growing evidence that OX40 activation can boost antitumor immune responses by modulating T-cell function (526–528).

Next Generation of Adoptive Cell Therapies

Our increasing knowledge of the immune system and how it interacts with cancer cells is rapidly being harnessed to expand on the number of approaches to eradicating cancer by the immune system. An approach that has already garnered lot of attention and has immense future potential is through amplifying the killing power of the immune system by providing more cancer-targeted immune cells (see sidebar on **How Immunotherapeutics Work,** p. 100).

One way to boost the killing power of immune cells called T cells is through adoptive T-cell therapy (see sidebar on **Types of Adoptive T-Cell Therapy,** p. 109). The goal is to dramatically increase the number of functional cancer-killing T cells in a patient. Three of these new types of immunotherapy have been approved by the FDA, Brexucabtagene autoleucel, axicabtagene ciloleucel and tisagenlecleucel. They are a type of CAR T-cell therapy approved for treating certain patients with hematological cancers. The treatment involves harvesting T cells from a patient's blood, expanding them in number, and genetically modifying them to target and kill cancer cells when infused back into the patient. Currently CAR T-cell therapy

involves a complex medical process that is customized for each individual patient. Many efforts are underway to facilitate the production of these therapeutics including the development of off-the-shelf and universal CAR T cells as well as to expand these treatments beyond blood cancers.

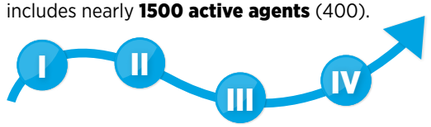
Researchers are currently investigating ways to make T-cell therapies more powerful and persistent. Some are looking to identify safe and effective uses of gene editing techniques such as CRISPR to knock out selected genes while also adding certain DNA into CAR T cells to make them better attack cancer cells and/or to enhance T-cell survival. For instance, one area of extensive investigation is the use of CRISPR to disrupt PD-1 in order to help T cells become more effective (529). This strategy is similar in concept to combining PD-1 checkpoint inhibition with adoptive T cells and may improve the clinical effect of CAR T or other adoptive T-cell therapy. A recent report demonstrated the ability of the CRISPR technique to successfully perform multiple genetic edits to the T cells. The process enabled edited T cells to sustain their ability to attack and kill tumors while surviving in the patients' bodies for several months (530). The clinical benefit of this method in terms of patient outcomes as well as long-term safety remains to be determined. Another exciting recent application of CRISPR in cancer immunotherapy has been in the genetic manipulation of cancers that leads to putting a tag on the tumor cells so that immune cells can find, attack, and eliminate them (531).

A second exciting approach to adoptive T-cell therapy is the use of tumor-infiltrating lymphocytes (TIL). Contrary to CAR T-cell therapy which uses circulating T cells in the blood, TIL therapy involves harvesting T cells from a patient's tumor, expanding them, and infusing them back into the patient. Therefore, the TIL approach utilizes T cells that may have already been primed to recognize and target a patient's tumor. The first evidence of the anticancer effects of TIL was demonstrated in the treatment of melanoma over three decades ago (532). Since then, the TIL approach has been shown to be effective in treating several other solid tumors including breast, colorectal, lung, and ovarian cancers (533–536). Numerous clinical trials are currently underway to evaluate the long-term survival benefits of TIL therapy, alone or in combination with other immunotherapies.

The number of adoptive cell therapies against cancer in preclinical and clinical development globally is expanding rapidly and, in fact, constitutes the largest number of agents currently in development in immunotherapy (400). While a majority of these efforts are centered around T cells, many researchers are trying to harness the function of other immune cells such as macrophages, dendritic cells, or natural killer (NK) cells to eradicate cancer (see sidebar on **Key Players in the Immune System,** p. 126) (537–539). NK cell therapy approaches have garnered much attention recently due to several lines of promising early preclinical and clinical evidence. For instance, in a recent clinical study, patients with certain types of leukemia or lymphoma demonstrated significant clinical responses, including some who achieved complete remission of their cancers, when treated with CAR expressing NK cells (539). The CARs on these NK cells were engineered to target the same CD19 protein on cancer cells that is used in CAR T cell therapies. Notably, treatment with CAR NK cells did not cause some of the toxic side effects that are often associated with CAR T therapy highlighting a potential advantage of the NK cell therapy approach. Ongoing research is investigating additional NK cell therapies employing novel CARs that are directed against distinct antitumor proteins. One strategy using a genetically engineered version of the receptor NKG2D is especially exciting since this receptor can interact with eight different proteins located on the surface of cancer cells, simultaneously (540). Such interactions may potentially enhance the specificity of NK cells toward cancer cells and thereby increase their cancer-cell-killing ability.

THE CURRENT GLOBAL CANCER CELL THERAPY PIPELINE

The current global cancer cell therapy pipeline includes nearly **1500 active agents** (400).



Immunotherapeutics have yielded extraordinary benefits for patients with a diverse array of cancer types, but because these therapeutics work by unleashing the power of the immune system, they are often associated with adverse and sometimes severe side effects. The immune-related adverse events can affect any organ in the body and range from minor rash and local inflammation that can be treated with steroids and/or by temporarily discontinuing the treatment, to more severe adverse effects like thyroiditis and diabetes that need lifelong treatment with thyroid medications and insulin, respectively (541). Understanding the serious adverse events including autoimmune diabetes, cardiotoxicity, and how to mitigate them is a crucial step in order to ensure positive outcomes for all patients, and it remains an area of intensive research investigation.

COMBATTING CANCER THROUGH SCIENCE-BASED, PATIENT-CENTERED POLICIES

IN THIS SECTION YOU WILL LEARN:

- Federal funding for medical research, most specifically through the NIH, NCI, and CDC, has a significant impact on our nation's health and the United States economy.
- Regulatory science initiatives at the FDA are vital to accelerating the progress against cancer.
- Policies and federally funded public health programs, many of which are supported by the 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.

This is both an exciting and uncertain time for cancer research. On the one hand, it is an extraordinary time, as new discoveries are changing the way we prevent, detect, diagnose, and treat cancer, bringing hope to patients and their loved ones. This progress would not be possible without years of public investment in medical research through the NIH. Congress has made a strong commitment to advancing medical science over the past five years, increasing NIH funding by 39 percent from FY 2015 to FY 2020. In particular, Senator Roy Blunt (R-MO), Senator Patty Murray (D-WA), Congresswoman Rosa DeLauro (D-CT), and Congressman Tom Cole (R-OK) have demonstrated remarkable leadership in their respective roles on the Labor-Health and Human Services (HHS)-Education Appropriations Subcommittees in the Senate and House, respectively.

Unfortunately, in 2020, the COVID-19 health and economic crisis has had a significant negative impact on medical research including cancer research. Across the country, many researchers had to put their work on hold as laboratories closed, accrual to clinical trials slowed, and resources were diverted to the COVID-19 response (see **Special Feature on Covid-19 and Cancer,** p. 27).

During these challenging times, we are fortunate that Congress continues to express its commitment for the critical role of NIH-funded research to fuel progress against cancer and other diseases. Similarly, the FDA has received strong bipartisan support in recent years. Funding for the FDA, including the Oncology Center of Excellence (OCE), is essential to ensure that research breakthroughs can be translated into safe and effective new treatments. Meanwhile, increased CDC funding is crucial to bringing evidence-based public health interventions, including cancer screening, to communities across the country.

According to NIH Director Francis Collins, MD, PhD, the coronavirus pandemic has caused over $10 billion in lost research, not to mention the additional unforeseen medical research needs posed by this virus. Therefore, in addition to robust annual budget increases, supplemental funding will be needed to reignite the research efforts that drive progress against cancer and other diseases.

MEDICAL RESEARCH: A WISE INVESTMENT FOR AMERICA

Annual investments in the NIH are the bedrock of the U.S. scientific enterprise, leading to discoveries that save lives, as discussed by **Congressman Peter King** (see p. 130). NIH-funded research grants have played a role in many of the major medical breakthroughs that are benefiting patients today, including much of the exciting progress described in this report (29). Thanks to strong bipartisan leadership in both the House and Senate, Congress has made medical research a top priority, increasing the NIH budget by a total of $11.6 billion over the last five years (see **Figure 21,** p. 132).

THE HONORABLE

PETER KING

AGE 76 | U.S. REPRESENTATIVE FOR
NEW YORK'S 2ND CONGRESSIONAL DISTRICT

Working to Support Cancer Research Funding and Access to Early Detection

Cancer has had a profound impact on my life through the experiences of my loved ones. My first family experience with cancer was in 1976, when my father was diagnosed with prostate cancer at age 60. He had never undergone an annual physical, and in those days most men didn't know about prostate cancer and never spoke about it. Though he still had a few intervals of seemingly good health, he passed away in 1982 after a lot of quiet suffering.

Since my father's diagnosis, many other close family members have battled cancer. In 1979, my niece was stricken with childhood cancer before she turned 3. Though she survived, the chemotherapy she received caused cardiomyopathy, and she had to have a heart transplant when she was 10 years old. My mother was diagnosed with breast cancer in 1986, when she was 69. She had a mastectomy and lived until she was 90. Her cancer never recurred. My brother was diagnosed with leukemia in 1996, when he was 49. He was treated with chemotherapy and has been in good health ever since. My daughter was diagnosed with breast cancer in 2018, when she was 45. She had a lumpectomy and radiation with no chemotherapy and is in excellent health.

I can't overstate the importance of early detection for cancer. I believe that early detection saved my daughter, mother, sister, and niece and would have saved my father if he had gone for a routine physical and paid attention to the obvious symptoms. After seeing what happened to my father, whom we all thought of as Superman, I started getting annual physicals. Because of a high PSA [prostate specific antigen], I have had a number of prostate biopsies, which have all been benign.

All of these experiences caused me to be very active in Congress supporting cancer research funding and working to make early detection of cancer available to as many people as possible. Federal investment in medical research is absolutely vital in saving lives. It is also important for our economy and creates good-paying American jobs.

It is extremely important that researchers and patient advocates share their stories on Capitol Hill. It is impactful to put a name and a face to a request. Members and congressional staff remember these stories when it comes time to decide which items or bills to support. The Dear Colleague letter in support of National Institutes of Health funding that I colead each year is a great example of the importance of advocacy. Countless groups ask members to support this letter, and it's a major reason why we get hundreds of member signatures from across the political spectrum. It is also interesting for members to get updates on cancer research from the scientists on the ground. It is particularly exciting to hear about work happening in their district or home state.

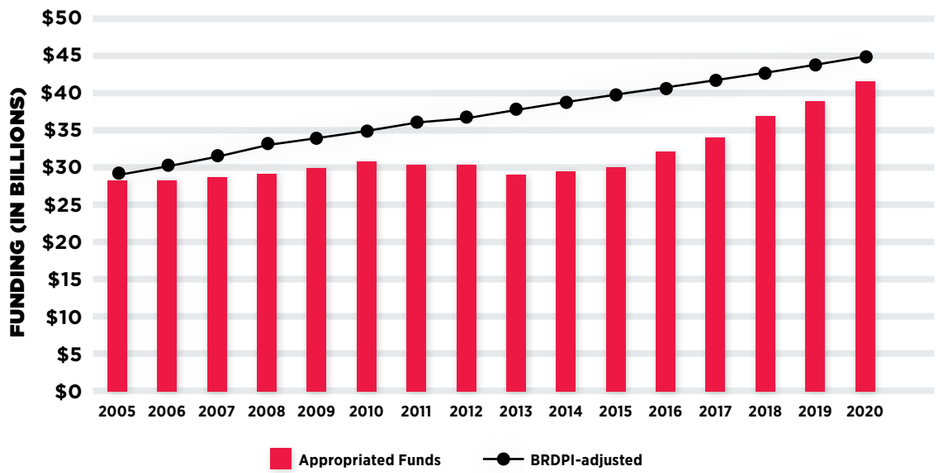
I am proud to serve as a cochair of the House Cancer Caucus and colead on the annual appropriations request for the National Cancer Institute. I also colead several funding requests related to cancer research at the Department of Defense, including those for the Peer-Reviewed Cancer Research Program and disease-specific research programs including breast, prostate, ovarian, and kidney cancers.

We must do all that we can to eliminate barriers to detection and treatment of cancer. I am the lead Republican sponsor of H.R. 2428, the Access to Breast Cancer Diagnosis Act, which would require insurance companies to cover breast cancer diagnostic tests the same as screenings. This is of particular importance to me given that my daughter's tumor was not discovered on a mammogram. I am also a cosponsor of H.R. 1570, the Removing Barriers to Colorectal Screening Act, which would require Medicare to cover the costs of removing polyps discovered during colorectal screenings. Additionally, I am a cosponsor of H.R. 1730, the Cancer Drug Parity Act, which would require oral cancer medications to be covered the same as i.v. medications.

I want to thank all of the scientists and physicians who have dedicated their careers to making progress against cancer. We all owe you a huge debt of gratitude. You have made a difference in every person's life and I can't wait to see what future research holds. After my retirement from Congress at the end of this session, I plan to continue advocating for cancer research in any way that I can. This cause is just too vital.

Federal investment in medical research is absolutely vital in saving lives.

FIGURE 21 NIH FUNDING: CONTINUING THE MOMENTUM FROM FIVE YEARS OF ROBUST INCREASES



Thanks to strong bipartisan leadership in Congress, the NIH has benefited from five consecutive years of strong funding increases. The biomedical research and development pricing index (BRDPI) reflects the rising cost to conduct medical research. Since fiscal year (FY) 2015, Congress has increased NIH funding by 39 percent, narrowing the gap between BRDPI levels and appropriated funds after several years of relatively stagnant growth.

The 21st Century Cures Act, bipartisan legislation passed by Congress in 2016, has also provided funding for the National Cancer Moonshot Initiative through the NIH Innovation Fund (see sidebar on **The National Cancer Moonshot Initiative,** p. 133). The National Cancer Moonshot Initiative is accelerating progress against cancer in specific priority areas where there is significant opportunity.

The level of enthusiasm for cancer research has perhaps never been higher, as demonstrated by an almost 50 percent increase in NCI grant applications over the past five years (542). While this tremendous interest is promising for the field of cancer research, it also represents a unique challenge for the NCI compared with other NIH institutes and centers, which have seen relatively stable application numbers over the same period. Given that the NCI's budget has not increased at the same rate as its investigator-initiated Research Project Grants (RPG) applications, there has been a recent trend of falling paylines and declining success rates for these grants. For example, in FY 2018, the payline for NCI R01 grants was 8 percent. The FY 2018 success rate for NCI applications was 12 percent, compared with 22 percent for the rest of NIH (543). Such low rates serve as a disincentive for researchers, particularly those earlier in their careers, to continue submitting grant applications to the NCI or to remain in the field of cancer research.

Congressional leaders did act to address this issue in the FY 2020 budget by providing a 5 percent funding increase for NCI, specifically including funds to increase the number of research grants funded in the year. Based on this allocation, the NCI announced that the payline for R01 grants would increase to 10 percent, the first time this figure has been in double digits since FY 2017 (544). While this was an important step, we also know that many promising proposals that could change the landscape of cancer are still being left unfunded. Continued funding increases for the NCI — and specifically for investigator-initiated RPG awards — is

THE NATIONAL CANCER MOONSHOT INITIATIVE

The 21st Century Cures Act, passed in 2016, authorized $1.8 billion over 7 years to fund the Cancer Moonshot, which has three overarching goals: to accelerate progress in our understanding of cancer, to encourage collaborations and partnerships, and to enhance data sharing.

To date, Congress has appropriated $1.195 billion, with which the NCI has launched a series of new scientific initiatives that directly address the goals of the Cancer Moonshot. Progress over the past 3 years has been substantial. In November of 2019, NCI hosted its first Cancer Moonshot collaborative meeting that offered the opportunity for hundreds of investigators, from across 9 different research networks with different expertise, to share results and exchange ideas in areas such as the tumor microenvironment, novel drug targets, emerging treatment approaches, and data integration and visualizations. To continue to foster communication, NCI is launching a new Cancer Moonshot seminar series that will continue to showcase its progress.

As findings of the Cancer Moonshot initiatives are published, we can expect to gain insights into cancer that will benefit patients, while giving investigators new avenues to pursue. These opportunities were made possible by decades of investment in basic science and sustained support for the entire cancer research enterprise.

Examples of new and ongoing Cancer Moonshot projects include:

- Using direct patient engagement approaches to promote participation in cancer genome sequencing programs to address knowledge gaps in our understanding of cancer, such as rare cancers and understudied populations
- Designing and testing approaches that enhance communication, collaboration, and coordination among different clinicians involved in the transition from treatment to follow-up care for cancer survivors to improve outcomes
- Improving colorectal cancer screening, follow-up, and referral for care among populations that have low colorectal cancer screening rates—particularly racial and ethnic minority populations and people living in rural areas
- Developing interventions to mitigate long-term adverse effects for pediatric, adolescent, and young adult cancer survivors
- Creating new experimental models for investigating how tumors resist therapies and for exploring ways to make cancers more sensitive to treatments
- Generating racially and ethnically diverse patient-derived models to understand disparities observed in the outcomes of cancer treatments
- Developing improved cancer immunotherapies that reduce immune-related adverse events
- Using advanced imaging technologies to create dynamic atlases of the multidimensional tumor ecosystem

NCI is currently planning new research opportunities for FY 2021. In addition, the Institute continues to provide opportunities for collaboration, data sharing, and outreach. For more information and updates, visit **cancer.gov/moonshot**
Adapted from (109)

critical to ensure continued progress. The NCI Director's FY 2021 Professional Judgement Budget Proposal calls for a total of $6.928 billion for the NCI, which would allow for a payline increase to 15 percent.

Most funds appropriated to the NIH by Congress are awarded to scientists in all 50 states and the District of Columbia through a competitive review process. Investments in the 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 in communities across the U.S. supported nearly 476,000 jobs and generated more than $81 billion in economic activity in FY 2019 (545).

Congress has made a clear and impactful commitment to medical research over the last five years, returning the NIH to a trajectory of steady funding growth. However, this is no time to stop. With so many opportunities to make progress against cancer and other diseases, it is as important as ever for our elected leaders to continue providing robust, sustained, and predictable increases for medical research funding.

Supporting a Strong, Diverse Research Workforce

Continued progress against cancer requires investment in the recruitment, training, and ongoing support of the next generation of cancer researchers. Early-career scientists are not only key to ensuring a strong pipeline of cancer researchers, but they are also responsible for bringing fresh ideas and innovative research questions to the field. To realize the full potential of our medical research enterprise, we must also ensure that the cancer research workforce reflects the diversity of our country, including diversity in race, ethnicity, gender, geography, and scientific discipline. The NIH and NCI play a large role in supporting young researchers who will become the scientific and clinical leaders of the future.

With the support of Congress, the NIH has prioritized advancing the careers of early-career researchers, including through the Next Generation Research Initiative. This program is focused on ensuring the long-term stability and strength of the U.S. medical research enterprise by supporting early-stage investigators and mid-career investigators through specific funding efforts.

The NCI has also implemented several additional policies and programs to support early-stage investigators. For example, for FY 2020 grant applications, the NCI has established a payline in the 15th percentile for early-stage investigators, compared with 10 percent for the general applicant pool. In addition, the NCI continues to convert the most meritorious R01 applications from early-stage investigators to Method to Extend Research in Time (MERIT) (R37) awards. This program, which was introduced in 2018, provides the opportunity to extend funding for an additional two years beyond the initial award period, allowing more time for these researchers to establish their careers before submitting renewal applications (544).

Notably, the COVID-19 crisis presents an enormous challenge for early-career researchers. Many young scientists have had their studies, fellowships, and initial projects severely disrupted by the pandemic, and are at risk of leaving the medical research field. As Congress considers both annual appropriations and supplemental funding, it will be vitally important to invest additional resources in support of these young researchers, on whom we are clearly depending for future breakthroughs against deadly diseases such as cancer.

ADVANCING REGULATORY SCIENCE AND POLICY

The FDA is a crucial part of the medical research enterprise. To fulfill its public health mission of assessing the safety and efficacy of medical products, the agency must stay abreast of the ever-accelerating rate of innovation demonstrated by cancer research. Achieving this mission will require consistent, robust support from Congress through annual appropriations. User fee agreements are a necessary and essential source of support to the agency, but appropriated dollars support vital regulatory science programs that advance regulatory policies and culminate in the scientifically informed, efficient, and expeditious review of oncology medical products.

The support that FDA receives is also vital to ensuring that the agency is able to keep pace with the technological advancements that are taking place throughout the industries that it is charged with regulating. Therefore, in 2019, the FDA unveiled the Technology Modernization Action Plan (TMAP). This plan outlines strategies for modernizing the agency's technological infrastructure, developing new technologies to support regulatory efforts, and communicating with stakeholders to drive interoperable technological progress. Through the execution of this plan, the agency aims to build an infrastructure that will support increased use of new technologies and data collection methods, enable the agency to better evaluate novel sources of data, and ensure that the potential benefits from new technologies and approaches are translated to patients in an even more expeditious time frame.

Additionally, the FDA has been preparing for the increased use of AI, both within the agency and in the applications for drugs and devices it reviews. AI algorithms have been explored to complement the analysis of scans collected to detect and monitor cancer. Combined with the experience of radiologists, these algorithms have the potential to improve the efficiency of cancer detection and diagnosis. AI has applications in helping scientists identify new cancer therapy candidates and clinical decision software used to support oncologists and other physicians. Many of these applications must be reviewed by the FDA to ensure the benefits they provide outweigh any risks. To successfully integrate and review AI, the FDA will need a modern technology infrastructure and a robust workforce with expertise in AI and related concepts. Such a workforce is vital to the agency's efforts to keep pace with modern technology.

As mandated by the 21st Century Cures Act and other legislation, the FDA is also seeking to understand and explore potential uses for real-world evidence in regulatory decision-making and has included it as an important aspect of the TMAP infrastructure revitalization effort. Real-world evidence is clinical evidence regarding the usage and potential benefits or risks of a medical product derived from analysis of data sources such as electronic health records, insurance claims data, and wearable health devices. Real-world evidence has been used to supplement randomized controlled trial data, particularly in cases of rare cancers or other diseases. Efforts to incorporate real-world evidence into regulatory decision-making are likely to take center stage as groups conducting cancer clinical trials and the FDA work together to overcome the impact of COVID-19 and consider ways to overcome the challenges posed by the lack of certain data from clinical trials that were adversely affected by the pandemic.

FDA is also taking steps to reorganize its workforce to allow its staff to become more efficient and to better understand the diseases and drugs that fall in their respective areas of review. For example, during the fall of 2019, the FDA Office of New Drugs increased the number of clinical review divisions from 19 to 27. A key piece of this reorganization was the restructuring of the Office of Hematology and Oncology Products into the Office of Oncology Diseases (OOD) and expanding from three clinical review divisions to six.

Established in 2017, the OCE was created to streamline the review of anticancer therapeutics and increase regulatory efficiency through collaboration between agency staff with oncology expertise from the medical product centers of the FDA — the Center for Drug Evaluation and Research (CDER), the Center for Biologics Evaluation and Research (CBER), and the Center for Devices and Radiological Health (CDRH). In 2019, the OCE approved 11 new anticancer therapeutics. In addition, despite the unprecedented effects of the COVID-19 pandemic and the resulting need for agency staff to engage in maximum telework for personal safety, the OCE approved over 40 new anticancer indications, including ten new anticancer therapeutics from March to July 2020.

Beyond coordinating the reviews of anticancer therapeutics, the OCE is focused on bringing stakeholders together to discuss, learn, and collaborate with the goal of advancing regulatory science. In September 2019, the OCE announced Project Orbis, a valuable initiative that provides a framework for drug approval applications to be submitted and reviewed concurrently by multiple international regulatory agencies. The FDA oncology products review division has long held regular, confidential teleconferences with other regulatory agencies to exchange information related to applications they are reviewing, and Project Orbis represents an extension of that collaboration to speed global drug review (see **Table 7,** p. 136).

In addition, the OCE is working to make patient-reported outcomes (PROs) from cancer clinical trials more accessible to the public. Although the FDA often receives and reviews PRO data as part of the drug approval process, it is rarely included in product labeling. Through a pilot website unveiled in June 2020, Project Patient Voice is a platform to provide patient-reported symptom data to the public in a standardized, easily digestible format (546). The OCE will refine the presentation of these data over time by incorporating stakeholder feedback.

ADVANCING EFFECTIVE CANCER PREVENTION, TREATMENT, AND CONTROL EFFORTS

To achieve the greatest benefits to public health, new medicines and technologies must reach all members of society. 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. For example, it is estimated that in the United States, HPV infection accounts for about 34,000 cases of cancer each year, including almost all cases of cervical cancer (see **Prevent and Eliminate Infection with Cancer-causing Pathogens,** p. 49). HPV vaccination is recommended for girls and boys ages 11 or 12 (see sidebar on **HPV Vaccination Recommendations,** p. 53). Although HPV vaccination rates among U.S. adolescents have risen in recent years, they remain significantly below the national goal of 80 percent set by the U.S. Department of Health and Human Services in Healthy People 2020 (121). 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 cancer prevention and screening, to increase vaccination rates, and to improve screening and treatment of precancerous HPV-related lesions.

The cancer advocacy and scientific communities continue to work with members of Congress, the NIH, the CDC, and other federal agencies to support and accelerate the elimination of HPV-related cancers in the United States

TABLE 7 ADVANCING REGULATORY SCIENCE THROUGH INTERNATIONAL COLLABORATION

Project Orbis offers a structure through which international regulatory agencies may accept concurrent submission and review of oncology products.

Indication (US Approved)	Generic Name	Trade Name	International Agencies Who Participated in Orbis Review
Certain type of liver cancer	Atezolizumab/Bevacizumab	Tecentriq/Avastin	
Certain form of lung cancer	Nivolumab/Ipilimumab (/platinum-doublet chemotherapy)	Opdivo/Yervoy	
Gastrointestinal stromal tumors	Ripretinib	Qinlock	
Certain leukemias	Ibrutinib(/rituximab)	Imbruvica	
Certain type of HER2+ breast cancer	Tucatinib (/traztuzumab/capecitabine)	Tukysa	
Certain types of leukemia and lymphoma	Acalabrutinib	Calquence	
Certain type of endometrial cancer	Pembrolizumab/Lenvatinib	Keytruda/Lenvima	
Certain form of lung cancer	Lurbinectedin	Zepzelca	
Certain type of colorectal cancer	Pembrolizumab	Keytruda	
Myelodysplastic syndromes	Decitabine/Cedazuridine	Inqovi	(unspecified others)
Certain melanomas	Atezolizumab (/cobimetinib/vemurafenib)	Tecentriq	

and globally through public policy. Despite advances in cancer research and care, there are persistent disparities in health outcomes for certain segments of the U.S. population, including racial and ethnic minorities, individuals of low socioeconomic status, and residents of rural areas (see sidebars **Which U.S. Population Groups Experience Cancer Health Disparities?** and **U.S. Cancer Health Disparities,** p. 16 and p. 15). Many drivers of cancer health disparities have been identified, and policy solutions are needed to help achieve health equity. State-level vaccination mandates to attend public schools have greatly reduced the incidence of diseases like measles, mumps, and pertussis. Unfortunately, only Hawaii, Rhode Island, Virginia, Puerto Rico, and Washington, DC, require HPV vaccination for school attendance. Connecticut and New York are pursuing bills to mandate HPV vaccines in 2020, but further efforts will be needed to achieve the goal of an 80 percent vaccination rate in the United States.

Racial and ethnic populations continue to be underrepresented in clinical trials for developing new anticancer therapeutics. Barriers to patient participation in clinical trials that need to be addressed include financial barriers, restrictive eligibility criteria, and lack of recruitment and information about and access to clinical trials. Public policies are also needed to support continued innovation and greater access to treatment and diagnostic options for all patients with cancer. Notably, the COVID-19 pandemic has adversely affected the conduct of cancer clinical trials. According to the NCI, the effect of the COVID-19 pandemic on trials varies. In regions with high numbers of COVID-19 cases, some sites halted enrolling new patients, while other sites had to seek approval for changes to the clinical trial protocols to accommodate patients and continue care (547).

Supporting Public Health Policies to Reduce the Use of Tobacco Products

Thanks to the implementation of nationwide comprehensive tobacco control initiatives, the smoking rate among U.S. adults declined from 20.9 percent in 2005 to 13.7 percent in 2018 (116). However, the use of e-cigarettes has increased dramatically over the past few years. Data have shown that the use of e-cigarettes increased from about 1 percent in 2011 to nearly 28 percent in 2019 (140). According to the 2019 National Youth Tobacco Survey (NYTS), more than 5 million middle and high school students reported having used e-cigarettes in the past 30 days and nearly one million reported daily use. This is especially concerning because data suggest that youth and young adults who use e-cigarettes are more likely to try combustible cigarettes later (137). The 2019 NYTS also indicated that current e-cigarette users reported that Juul was their usual brand. Cartridge-based e-cigarettes, such as Juul, are available in very high nicotine content; have appealing flavors; and can be easily concealed and used discreetly. Many public health experts believe that youth and young adult e-cigarette use has reached an epidemic proportion. Given the alarming rates of use, many organizations have called for more action to protect youth and young adults from addiction to nicotine and the detrimental health effects of e-cigarette use. In December 2019, the president signed legislation raising the federal minimum age for sale of tobacco products, including e-cigarettes, from 18 to 21 years. While the passing of "Tobacco 21" was an important step, public health advocates want more to be done.

In January 2020, the FDA issued a final guidance outlining the agency's enforcement priorities for electronic nicotine delivery systems (ENDS). Under this policy, companies were ordered to cease the manufacture, distribution, and sale of flavored cartridge-based e-cigarettes with the exceptions of tobacco and menthol flavors. Unfortunately, disposable ENDS products were not included in the flavor ban and are still available in flavors targeted towards children.

Nearly all tobacco use begins in youth and young adulthood, and 95 percent of adult smokers began smoking before they turned 21. Therefore, we recognize that Tobacco 21 is one among several important federal policy changes that are important to address the public health crisis of e-cigarette use among U.S. youth and young adults. An additional important step involved a July 2019 order by the U.S. District Court for the District of Maryland requiring manufacturers of e-cigarettes, cigars, and other new tobacco products that were on the market as of August 8, 2016, to submit applications to the FDA for premarket review by May 12, 2020. While the FDA pushed back the deadline because of the coronavirus pandemic, therefore delaying the deadline to September 2020, tobacco companies are required to submit a Premarket Tobacco Product Application (PMTA) for any new tobacco product, including e-cigarettes, that demonstrates the product is appropriate for the protection of public health. Other potential actions to protect public health include prohibiting the manufacture and sale of all flavored tobacco products for disposable and open-tank devices available to youth (unless they are FDA-approved to aid in tobacco cessation for adult users); strongly supporting the actions that FDA's Center for Tobacco Products is taking to regulate the manufacturing, distribution, and marketing of tobacco products; and increasing funding for the prevention and cessation activities that are supported by the CDC Office on Smoking and Health.

POLICIES THAT STIMULATE PROGRESS AGAINST PEDIATRIC CANCER

Cancer remains the second leading cause of death among U.S. children ages 1 to 14. Research-fueled advances against pediatric cancer have increased the five-year relative survival rate for children diagnosed with cancer from 63 percent in the mid-1970s to 85 percent (2). Despite the progress, almost 1,200 children are expected to die of cancer in 2020. In addition, children who survive cancer often face health issues later in life. Recently enacted federal policies and programs are playing a key role in addressing the challenges faced by children with cancer and their families.

A recent initiative that has received strong support from Congress is the Childhood Cancer Data Initiative (CCDI), which focuses on the critical need to collect, analyze, and share data to address the burden of cancer in children, adolescents, and young adults (AYAs). The initiative supports maximizing the use and benefit of data from childhood and AYA cancer research for patients and survivors, and aims to make it easier for researchers to learn from each of the approximately 16,000 children and adolescents diagnosed with cancer in the United States each year. The CCDI is a federal investment of $50 million proposed to be extended in equal amounts per year for the next 10 years. The first year of the initiative was funded in December 2019.

On August 18, 2017, key provisions of the Research to Accelerate Cures and Equity (RACE) for Children Act were signed into law as part of the FDA Reauthorization Act of 2017. The RACE Act requires that drug developers study molecularly targeted therapeutics that they developed for adult populations in pediatric populations. This

applies to therapeutics that target molecules that fuel cancer development in both pediatric and adult patients. To facilitate this process, the RACE Act obligated the development of a Pediatric Molecular Targets List detailing molecular targets that do and do not meet the criteria. As of August 18, 2020, applications submitted to the FDA for therapies meeting RACE Act criteria must have agency-approved pediatric study plans.

The Childhood Cancer Survivorship, Treatment, Access, and Research (STAR) Act, signed into law in June 2018, is the most comprehensive childhood cancer legislation passed by Congress to date. This legislation includes provisions to improve childhood cancer surveillance, enhance research on the late effects of childhood cancers, and increase research opportunities by expanding the collection of biospecimens for childhood cancer patients.

The STAR Act provisions are being implemented across multiple agencies. For example, the NCI has already issued two requests for applications for research proposals focused on improving care and health-related quality of life for childhood, adolescent, and young adult cancer survivors. Numerous grants have been supported in the first round of funding, which was issued in 2019, with the second round to be funded in 2020. Meanwhile, the CDC has expanded support for childhood cancer surveillance in 10 states and is working to partner with more states to improve collection of this vital information. The Government Accountability Office is currently conducting an extensive report on barriers that impede access to care for childhood cancer survivors, and the Agency for Healthcare Research and Quality is developing national standards of care for childhood cancer survivors based on research of best practices.

All of these components are critical to increasing our understanding of childhood cancers and the best ways to support survivors as they transition to adulthood and beyond. Further progress will depend on Congress continuing to appropriate annual funding for STAR Act implementation in accordance with the legislation ($300 million total over 10 years).

The Gabriella Miller Kids First Pediatric Research Program (Kids First) at the NIH is supporting new discoveries in the biology of childhood cancer and the links to birth defects. Funding for this program was established in the Gabriella Miller Kids First Research Act, passed by Congress in 2014. Since that time, $75 million have been invested in pediatric research. The Gabriella Miller Kids First Research Act 2.0 was introduced in April 2020 by Reps. Jennifer Wexton (D-VA), Tom Cole (R-OK), Peter Welch (D-VT), and Gus Bilirakis (R-Fl). This legislation redirects certain penalties against pharmaceutical companies for specified violations to the 10-Year Pediatric Research Initiative Fund, an existing fund that supports pediatric disease research. The NIH will make allocations from this fund to support lifesaving pediatric research that does not duplicate existing activities.

THE AACR CALL TO ACTION

Medical research is spurring scientific and technological innovation that is driving progress against the many diseases we call cancer. Thanks to remarkable bipartisan efforts in Congress the NIH budget has grown significantly in the past five years, allowing our nation's researchers to capitalize on many of the unprecedented scientific opportunities that exist today to improve health and save lives.

In addition to making medical research a national priority, Congress has acknowledged the need for increased innovation at the FDA to ensure the rapid translation of research discoveries into safe and effective treatments, and swift dissemination of these treatments to patients who need them urgently. Furthermore, Congress recognizes the vital role of an active CDC to protect our citizens from serious health threats.

During this unprecedented time in our nation's history, there is also a need for our nation's leaders to take on a much bigger role in confronting and combatting the structural and systemic racism that contributes to health disparities. Renewed attention has been drawn to the issue of pervasive racism and social injustices in light of the COVID-19 pandemic as well as the recent atrocities against people of color. Likewise, it is time for the scientific community to step up, and partner with Congress to assess and address this issue within the research community.

THEREFORE, THE AACR URGES CONGRESS TO:

- Continue to support robust, sustained, and predictable growth for the NIH and NCI by providing increases in their FY2021 base budgets of at least $3 billion and $522 million, respectively, for a total funding level of $44.7 billion for the NIH and $6.9 billion for the NCI.
- Ensure that the $195 million in funding designated through the 21st Century Cures Act for targeted initiatives, including the National Cancer Moonshot, is fully appropriated in FY2021 and is supplemental to the overall increase in the NIH base budget.
- Support the FDA's critical regulatory science initiatives by providing an increase of at least $120 million in discretionary budget authority in FY 2021.
- Support the 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.
- Continue to support appropriation bills that include increased funding for CDC's Office of Smoking and Health, to continue to strengthen comprehensive tobacco prevention and control programs.
- Provide $50 million for the second year of the Childhood Cancer Data Initiative and "no less than" $25 million for the continued implementation of the Childhood Cancer STAR Act.
- Exempt NIH and other key public health agencies from the highly restrictive FY 2021 budget caps to allow them to forcefully respond to the COVID-19 health crisis, as well as to support the science that is necessary to improve and save lives from the myriad of diseases faced by Americans and by people all over the world.
- Eliminate the pervasive racial biases in the conduct of cancer research that have led to significant inequities in cancer care, low participation for minorities in clinical trials, and an underrepresentation of racial and ethnic minority scientists in the cancer research workforce by supporting a congressional effort that calls on the National Academies of Science, Engineering, and Medicine to undertake a study to assess systemic racism in academia.

The COVID-19 pandemic is one of the greatest health crises that this country has ever faced, leading to thousands of lives lost, an economy thrown into chaos, and significant alterations in everyday life for millions of Americans. The pandemic has also highlighted the vital importance of medical research. Across the country, funding for ongoing medical research was diverted to stop the spread of COVID-19 and to expeditiously develop vaccines and treatments for this unprecedented disease.

In the face of the current health crisis due to the COVID-19 pandemic, cancer and other diseases continue to be major ongoing challenges. If we hope to reach the day when cancer is no longer a major health threat to our nation's citizens, Congress must provide the critical funding that is essential for research supported by the NIH and NCI. By providing robust, sustained, and predictable annual funding increases for the NIH and NCI in FY 2021 and beyond, Congress will accelerate the pace at which we make future scientific advances, capitalize on prior investments in cancer research, spur innovation and economic prosperity for our country, and bring lifesaving cures to many patients in the United States and around the world.

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GLOSSARY

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.

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 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.

Big data Data sets that are too large and complex for processing by traditional database management tools.

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 NIH budget must change to maintain purchasing power. The BRDPI is updated annually.

BRAF The BRAF protein is generated from the BRAF gene. It is found inside certain cell types, where it is involved in sending signals that direct cell proliferation. Mutations in the BRAF gene have been associated with various cancers, including some non-Hodgkin lymphomas, colorectal cancers, melanomas, thyroid cancers, and lung cancers.

BRCA1/2 (Breast Cancer Resistance 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.

Bruton tyrosine kinase (BTK) The BTK protein is generated from the BTK gene. It is found inside certain cell types—in particular, B cells (see B cell)—where it is involved in signaling pathways (see Signaling pathway/signaling network) that promote cell survival and multiplication. These signaling pathways are very important for survival of cancers arising in B cells, including chronic lymphocytic leukemia and mantle cell lymphoma.

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.

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.

GLOSSARY

Chemotherapy The use of drugs 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.

Cutaneous squamous cell carcinoma Cancer that begins in cells that form the outer layer of the skin, epidermis.

Cytotoxic An agent or substance that is toxic to living cells.

Death rate/mortality rate The number of deaths in a certain group of people in a certain period of time. Death rates may be reported for people who have a certain disease; who live in one area of the country; or who are of a certain gender, age, or ethnic group.

Deoxyribonucleic acid (DNA) The molecules inside cells that carry genetic information and pass it from one generation to the next.

Diffuse intrinsic pontine glioma A rare, fast-growing tumor that forms in cells called glial cells in a part of the brain stem called the pons. These tumors usually occur in children. They tend to spread to nearby tissue and other parts of the brain stem, are hard to treat, and have a poor prognosis.

DNA mismatch repair DNA mismatch repair is a system for recognizing and repairing erroneous insertion, deletion, and misincorporation of bases that can arise during DNA replication and recombination, as well as repairing some forms of DNA damage.

Electronic cigarette (e-cigarette) A battery-powered device that delivers nicotine by vaporizing a nicotine solution, rather than by combusting tobacco as do traditional cigarettes and cigars.

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.

Epithelioid sarcoma A type of soft tissue sarcoma. These are rare cancers that usually begin as a slow-growing, firm lump in the deep soft tissue or skin of the arms, hands, or fingers. They may also occur in the legs, chest, abdomen, or head and neck. Epithelioid sarcoma may spread to nearby tissue, lymph nodes, or other parts of the body. It often comes back after treatment. They are more common in young adults.

Five-year survival rate The percentage of people in a specific group, for example, people diagnosed with a certain type of cancer or those who started a certain treatment, who are alive 5 years after they were diagnosed with or started treatment for a disease, such as cancer. The disease may or may not have come back.

Gene The functional and physical unit of heredity passed from parent to offspring. Genes are pieces of DNA and most genes contain the information for making a specific protein.

Hepatocellular carcinoma (HCC) HCC is the most common type of liver cancer. It occurs mostly in people with chronic liver diseases, such as cirrhosis caused by infection with hepatitis B virus or hepatitis C virus.

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.

Homologous recombination deficiency (HRD) A type of deficiency in a cell that impairs the ability of the cell to repair DNA by a process called homologous recombination. The process of homologous recombination is one of the ways in which a cell repairs DNA that has been damaged in both strands at the same time. Deficiencies in homologous recombination have been strongly linked to cancer development because decreased rates of homologous recombination can cause inefficient DNA repair. Tumors with a homologous recombination deficiency are described as HRD-positive.

Human papillomavirus (HPV) A type of virus that can cause abnormal tissue growth (e.g., warts) and other changes to cells. Infection for a long time with certain types of HPV can cause cervical cancer. HPV also plays a role in some other types of cancer, including anal, oropharyngeal, penile, vaginal, and vulvar cancers.

Immune 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.

Leukemia Cancer that starts in blood-forming tissue, such as the bone marrow, and causes large numbers of blood cells to be produced and enter the bloodstream.

Mammogram An X-ray of the breast that is used to look for early signs of breast cancer.

Melanoma Cancer that begins in melanocytes (cells that make the pigment melanin). These cancers may arise in a mole (skin melanoma), but they can also originate in other pigmented tissues, such as the eye (uveal melanoma) or the intestines (mucosal melanoma).

Metastasis The spread of cancer from one part of the body to another. A tumor formed by cells that have spread is called a metastatic tumor or a metastasis. The metastatic tumor contains cells that are like those in the original (primary) tumor. The plural form of metastasis is metastases.

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.

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.

GLOSSARY

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.

NTRK gene fusion A genetic alteration that occurs when a piece of the chromosome containing a gene called NTRK breaks off and joins with a different gene on another chromosome. NTRK gene fusions lead to abnormal proteins called TRK fusion proteins, which may cause cancer cells to grow. NTRK gene fusions are associated with many types of cancer, including cancers of the brain, head and neck, thyroid, soft tissue, lung, and colon. Also called neurotrophic tyrosine receptor kinase gene fusion.

Oncology The branch of medicine that focuses on cancer diagnosis and treatment.

Pandemic An outbreak of a disease that occurs over a wide geographic area across international boundaries and affects an exceptionally high proportion of the population.

Pancreatic cancer A group of cancers that start in cells of the pancreas, an organ located behind the stomach. Most pancreatic cancers begin in cells that make the digestive fluids, and the most common of these cancers are called adenocarcinomas. Cancers that arise in the pancreatic cells that help control blood sugar levels are called pancreatic neuroendocrine tumors.

Pathogen A bacterium, virus, or other microorganism that can cause disease. Also referred to as an infectious agent.

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.

Poly (ADP-ribose) polymerase (PARP) A type of protein involved in the repair of DNA damage. DNA damage may be caused by various factors such as normal cell actions, UV light and radiation, and some anticancer drugs. Inhibitors of PARP are used in the treatment of certain breast and ovarian cancers.

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.

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.

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).

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.

ROS1 gene fusion The ROS1 protein is a receptor tyrosine kinase (encoded by ROS1 gene). The role of ROS1 in normal development is not fully understood; however, genetic rearrangements of ROS1 have been identified in many cancers and widely studied in non-small cell lung cancer. These rearrangements create fusion proteins in which the kinase function of ROS1 becomes constitutively active and drives cellular multiplication. ROS1 fusions have been detected in multiple other cancer types in addition to lung cancer, including glioma, ovarian carcinoma, sarcoma, and cholangiocarcinoma, among others.

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.

Small cell lung cancer A fast-growing cancer that forms in tissues of the lung and can spread to other parts of the body. The cancer cells look small and oval-shaped when looked at under a microscope.

Soft tissue sarcoma A group of cancers that arise in soft tissues of the body such as the muscles, tendons, fat, blood vessels, lymph vessels, nerves, and tissues around joints. Both children and adults can develop soft tissue sarcomas. Rhabdomyosarcoma is the most common type of soft tissue sarcoma in children, while gastrointestinal stromal tumors are the most common in adults.

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 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.

TRK proteins A family of proteins that are found on nerve cells. They are involved in cell signaling pathways that control cell growth, cell maturation, and cell survival. In some patients with cancer, the genes that make the TRK proteins, NTRKs, may have alterations that cause abnormal TRK proteins to be made. These abnormal proteins may be too active or found in higher than normal amounts on some types of cancer cells, which may cause cancer cells to grow. Also called tropomyosin receptor kinase protein family.

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.

Tumor mutational burden (TMB) The total number of mutations found in the DNA of cancer cells. TMB of a patient's tumor can be used as a biomarker to help plan the best treatment option. For example, tumors that have a high number of mutations appear to be more likely to respond to certain types of immunotherapy.

Urothelial cancer The most common type of bladder cancer. It begins in urothelial cells that line the inside of the bladder.

*This list contains some of the specialized terms pertinent to the *AACR Cancer Progress Report 2020*.

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 tamoxifen	Evista 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	ingenol mebutate fluorouracil diclofenac sodium 5-aminolevulinic acid + photodynamic therapy (PDT) masoprocol/nordihydroguaiaretic acid	Picato Adricil Voltaren 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

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
multiple cancers	mechlorethamine hydrochloride	Mustargen
multiple cancers	melphalan	Alkeran
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

Increasing Precision

Cell Cytoskeleton–modifying Agents

Approved Indication	Generic Name	Trade Name
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

* 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.

Table continued on next page

SUPPLEMENTAL TABLE 2 *(continued)*
FDA-APPROVED THERAPEUTICS FOR THE TREATMENT OF CANCER

Antinutrients

Approved Indication	Generic Name	Trade Name
certain leukemias	asparaginase	Elspar; Kidrolase
certain leukemias	calaspargase pegol-mknl	Asparlas

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 neuroendocrine 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
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	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

Increasing Precision

* 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.

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SUPPLEMENTAL TABLE 2 *(continued)*
FDA-APPROVED THERAPEUTICS FOR THE TREATMENT OF CANCER

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 type of skin cancer	cemiplimab-rwlc	Libtayo
certain types of bladder cancer and lung cancer	durvalumab	Imfinzi
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
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 types of non-Hodgkin lymphoma	mogamulizumab-kpkc	Poteligeo
certain type of leukemia	moxetumomab pasudotox-tdfk	Lumoxiti
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	axicabtagene ciloleucel	Yescarta
certain types of leukemia and non-Hodgkin lymphoma	tisagenlecleucel	Kymriah
certain type of non-Hodgkin lymphoma	autoleucel brexucabtagene	Tecartus

Increasing Precision

* includes companion diagnostic
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SUPPLEMENTAL TABLE 2 *(continued)*
FDA-APPROVED THERAPEUTICS FOR THE TREATMENT OF CANCER

Cell-signaling Inhibitors

Approved Indication	Generic Name	Trade Name
certain type 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 gastrointestinal stromal tumor	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
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
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 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 type of breast cancer	ribociclib	Kisqali
gastrointestinal stromal tumor	ripretinib	Qinlock
myelofibrosis	ruxolitinib	Jakafi
certain type of breast 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
multiple cancers	trametinib	Mekinist
HER2+ breast cancer	trastuzumab	Herceptin
kidney cancer	temsirolimus	Toricel; Torisel
certain type of breast cancer	tucatinib	Tukysa
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

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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 US
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 are 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

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