AACR CANCER PROGRESS REPORT **2018**

HARNESSING RESEARCH DISCOVERIES FOR PATIENT BENEFIT

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American Association for Cancer Research®
FINDING CURES TOGETHER®

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TABLE OF CONTENTS

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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 all cancers. AACR membership includes more than 40,000 laboratory, translational, and clinical researchers; population scientists; other health care professionals; and patient advocates residing in 120 countries. The AACR marshals the full spectrum of expertise of the cancer community to accelerate progress in the prevention, biology, diagnosis, and treatment of cancer by annually convening more than 30 conferences and educational workshops, the largest of which is the AACR Annual Meeting with more than 22,500 attendees. In addition, the AACR publishes eight prestigious, peer-reviewed scientific journals and a magazine for cancer survivors, patients, and their caregivers. The AACR funds meritorious research directly as well as in cooperation with numerous cancer organizations. As the Scientific Partner of Stand Up To Cancer, the AACR provides expert peer review, grants administration, and scientific oversight of team science and individual investigator grants in cancer research that have the potential for near-term patient benefit. The AACR actively communicates with legislators and other policy makers about the value of cancer research and related biomedical science in saving lives from cancer.

For more information about the AACR, visit **AACR.org.**

A MESSAGE FROM THE AACR

There has never been a time of greater excitement in the cancer field. Thanks to advances in research, we are altering the trajectory of the devastating collection of diseases we call cancer. Research has spurred progress in public health and improvements across the cancer care spectrum that are reducing overall cancer incidence and death rates and increasing the number of people who are living longer, higher quality lives after a cancer diagnosis. Moreover, we are poised to drive forward and catalyze breakthroughs that will save more lives from cancer.

The *AACR Cancer Progress Report 2018* provides a comprehensive overview of the progress we are making because of research, much of which is supported by federal investments in the National Institutes of Health (NIH) and National Cancer Institute (NCI). As highlighted in the report, the pace at which basic research is deepening our knowledge of the complexities of cancer and the rate at which we are harnessing this knowledge to develop new and better approaches to cancer prevention, early detection, diagnosis, and treatment are accelerating for the benefit of cancer patients.

One of the areas of cancer treatment in which we are making extraordinary progress is immunotherapy. In the past decade, the number of immunotherapeutics has increased almost five-fold, and the number of cancer types that can be treated by at least one immunotherapeutic has more than tripled.

The most recent immunotherapeutics to enter the clinic, CAR T–cell therapies, took us across another medical frontier because they are generated by genetic engineering of a patient's own immune cells to attack the patient's cancer cells. Expanding our knowledge about the immune system and how it interacts with cancer cells, and facilitating the convergence of experts from an increasingly diverse array of disciplines will allow us to make even more pioneering advances in immunotherapy for the benefit of patients in the United States and around the world.

Discoveries in the field of cancer genomics are continuing to fuel the development of new molecularly targeted therapeutics, which are transforming the treatment of more and more types of cancer. As we step further into the era of precision medicine, the scope of progress will continue to broaden, providing new hope for many cancer patients who are awaiting more effective treatment options.

Despite the significant strides 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 609,000 lives in the United States this year. This number is predicted to increase considerably in the coming decades—because cancer is largely a disease of aging, and the segment of the U.S. population age 65 and older is growing—unless we develop and effectively implement new and even more effective strategies for cancer prevention, early detection, diagnosis, and treatment.

Moving forward, we also need to ensure that everyone benefits from groundbreaking advances against cancer. Cancer can strike anyone—no age, gender, race, ethnicity, socioeconomic status or political affiliation makes you immune to these devastating diseases. However, as highlighted in the report, advances against cancer have not benefited everyone equally, and certain segments of the population shoulder a disproportionate burden of cancer. This is unacceptable, and it is imperative that all stakeholders in the research community work together to more fully understand the reasons for cancer health disparities and then immediately develop and implement plans to eliminate them.

We have never been in a better position to take lifesaving cancer science from the bench to the clinic. We have the scientific knowledge, cutting-edge technologies, and capability to deliver a new wave of innovations that will transform cancer care. We also have bipartisan leadership in Congress that has delivered three consecutive years of steady, significant annual funding increases for biomedical research through the NIH, which will help us take advantage of these unprecedented opportunities.

Ensuring that biomedical research remains a high priority for our nation's policy makers is vital if we are to further accelerate our pace of progress. Thus, the AACR urges our elected leaders to continue to support robust, sustained, and predictable annual growth of the NIH budget, and to provide consistent and sufficient annual funding for the U.S. Food and Drug Administration (FDA) and the Centers for Disease Control and Prevention (CDC). These actions will guarantee that we take major strides toward realizing the goal of fundamentally changing the face of cancer at the earliest possible time.

Elizabeth M. Jaffee, MD
AACR President

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

EXECUTIVE SUMMARY

This is an incredibly exciting time for cancer research. The rapid pace and broad scope of the progress we are making against the collection of diseases we call cancer are extraordinary. This progress is being driven by research that both expands our understanding of all types of cancer and allows us to translate this knowledge into new and increasingly precise ways to prevent, detect, diagnose, treat, and cure a number of these diseases.

As the first and largest professional organization in the world dedicated to advancing every aspect of cancer research, the American Association for Cancer Research (AACR) is committed to increasing public understanding of cancer and the importance of cancer research for saving lives. It is also advocating for increased annual federal funding for 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 eighth edition of the report highlights how research discoveries continue to extend and improve lives, like the lives of the courageous individuals featured in the report who have shared their personal experiences with cancer. It also underscores how unwavering, bipartisan support from Congress, in the form of robust, sustained, and predictable annual increases in funding for the NIH, NCI, FDA, and CDC is vital if we are to save more lives from cancer.

ELIZABETH M. JAFFEE, MD
AACR PRESIDENT, 2018–2019

"During the almost 30 years since I began my fellowship in oncology, we have made unprecedented progress against cancer. These advances occurred largely because of tremendous progress in basic research."

CANCER IN 2018

Research continues to be our best defense against cancer. It spurs the development of new and better approaches to cancer prevention, detection, diagnosis, and treatment, which are driving down overall U.S. cancer incidence and death rates and increasing the number of children and adults who are living longer, higher quality lives after a cancer diagnosis. For example, the age-adjusted U.S. cancer death rate decreased by 26 percent from 1991 to 2015, a reduction that translates into almost 2.4 million cancer deaths avoided. In addition, the number of children and adults living in the United States with a history of cancer has reached a record high of more than 15.5 million.

From 2011 to 2015, overall cancer death rates fell by:

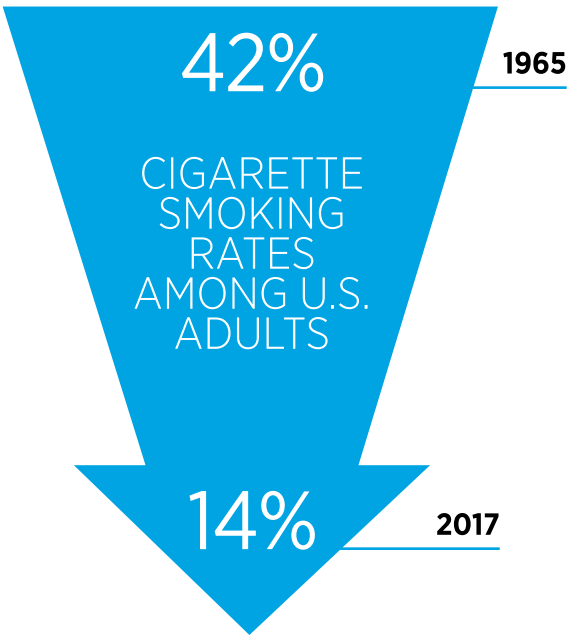
- 1.8% per year for U.S. men
- 1.4% per year for U.S. women
- 1.5% per year for children ages 0 to 14

Even though we are making significant progress, cancer continues to pose enormous public health challenges in the United States and around the world. One challenge is that the number of people diagnosed with cancer each year is projected to increase dramatically in the coming decades, with an anticipated rise from 1,735,350 in 2018 to 2,387,304 in 2035 in the United States alone. This is largely because cancer is primarily a disease of aging, and the segment of the U.S. population age 65 and older is growing. Another pressing challenge is that the burden of cancer is shouldered disproportionately by certain segments of the population, including racial and ethnic minorities and patients of lower socioeconomic status.

The immense toll of cancer is felt through the number of lives it affects each year and through its significant economic impact. The direct medical costs of cancer care, which are only one part of the financial impact of cancer, are estimated to have been $80.2 billion in the United States in 2015, the most recent year for which these data are available. With the personal and economic burden of cancer predicted to increase substantially in the next few decades, it is clear that the research that powers progress against cancer is a vital national investment.

PREVENTING CANCER: IDENTIFYING RISK FACTORS

Decades of basic, epidemiologic, and clinical research have led to the identification of numerous factors that increase a person's chance of developing cancer. Given that exposure to several of these factors can be avoided, many cases of cancer could potentially be prevented. In fact, it is estimated that more than four out of 10 cancer cases diagnosed in the United States are attributable to preventable causes.



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

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. For example, such initiatives drove down cigarette smoking rates among U.S. adults by two-thirds. However, some individuals do not take necessary preventive actions to lower their risks of cancer. Thus, we must identify new strategies to enhance the dissemination and implementation of our current knowledge of cancer prevention.

SCREENING FOR EARLY DETECTION

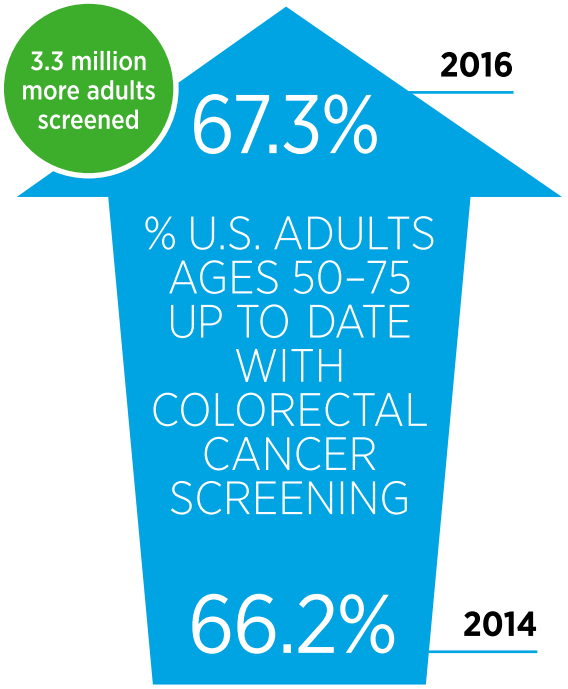
Research discoveries providing insight into the complexities of cancer initiation and progression are the foundation of screening strategies to detect, if present, precancerous lesions or cancer at an early stage of development. Finding precancerous lesions or cancer at an early stage of development makes it more likely that a cancer can be intercepted and that a patient can be 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 but who are at risk for the disease. Determining whether broad implementation of a cancer screening test across the 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.

Each person's risks for developing each type of cancer, tolerance of the potential risks of a screening test, and general health are unique. Therefore, every individual should consult with his or her health care practitioners to develop a personalized cancer prevention and early detection plan.

HARNESSING RESEARCH DISCOVERIES FOR PATIENT BENEFIT

The dedicated efforts of individuals working throughout the cycle of biomedical research are driving advances across the continuum of clinical cancer care. In recent years, the cycle has become increasingly efficient, accelerating the pace at which research discoveries are converted to lifesaving advances for people around the world.



Among the advances made from August 1, 2017, to July 31, 2018, are the 14 new anticancer therapeutics approved for use by the FDA. During this period, the uses of 11 previously approved anticancer therapeutics were expanded by the FDA to include additional types of cancer.

Two of the new anticancer therapeutics approved by the FDA are providing oncologists with a new way to use radiotherapy to treat neuroendocrine tumors. This approach is benefiting many patients, including **Nicole DiCamillo** (see p. 64).

Nine of the other 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 **Chuck Dandridge, Lisa Quinn**, and **Ron Scolamiero** (p. 68, 76, and 78, respectively).

Another two of the new anticancer therapeutics are revolutionary immunotherapeutics called CAR T–cell therapies. These transformative immunotherapeutics have been shown to yield remarkable and durable responses for some patients with blood cancers, as highlighted in the report by the experiences of **Tori Lee** and **Mike Delia** (p. 84 and 86, respectively).

The 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. Despite this progress, cancer survivors often face serious and persistent adverse outcomes, including physical, emotional, and psychosocial challenges, as a result of their disease and treatment. Palliative care, given alongside cancer treatment and throughout the balance of life, is one approach that can improve quality of life for patients and survivors.

LOOKING TO THE FUTURE

The incredible progress we have made against cancer is founded on research that has provided us with a deep understanding of cancer biology.

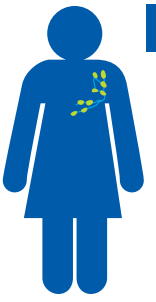
As we look to the future, many researchers, including **AACR President Elizabeth M. Jaffee, MD**, (p. 104), are confident that we will be able to accelerate the pace of progress against cancer by increasing collaboration between cancer researchers and experts from other disciplines such as mathematics, physics, chemistry, engineering, and computer science. The new wave of innovations driven by this convergence science approach will allow us to integrate and harness patient data to achieve the full potential of precision medicine. In addition, the incorporation of new technologies such as liquid biopsies and artificial intelligence will provide tools to address a wide range of clinical questions across the spectrum of precision cancer care.

If we seize these opportunities to drive science forward, we can stimulate breakthroughs that will save more lives from cancer.

BETWEEN AUGUST 1, 2017, AND JULY 31, 2018, THE FDA APPROVED:

14 **new** anticancer therapeutics, which are bolstering the pillars of cancer care.

11 **previously approved** anticancer therapeutics for treating new types of cancer.



1 **new** surgery guiding system.

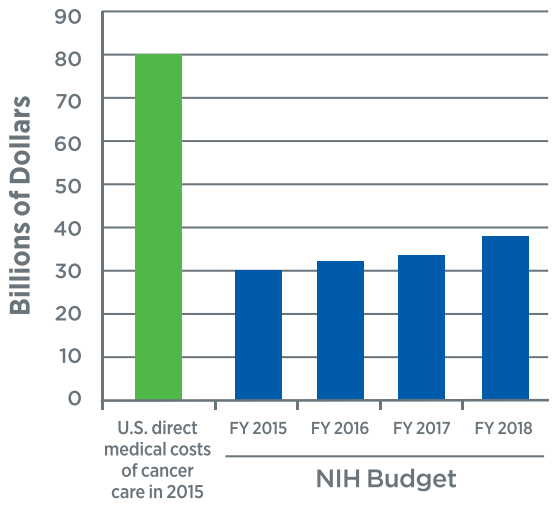
WORKING TOGETHER TO OVERCOME CANCER THROUGH SCIENCE-BASED, PATIENT-CENTERED PUBLIC POLICY

Federal investment in the NIH, NCI, FDA, and CDC has spurred 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, robust, sustained, and predictable annual budget increases for NIH and NCI are necessary, as is support for vital initiatives like the National Cancer Moonshot. We must also continue our nation's commitment to supporting a strong FDA, as well as 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 advance cancer prevention, early detection, and control for individuals, families, and communities.

DIRECT COSTS OF CANCER CARE ARE STARTLING

The costs of treating a single disease stand in stark contrast to the entire NIH budget.



THE AACR CALL TO ACTION

Thanks to remarkable, bipartisan efforts in Congress, the NIH budget is back on a trajectory of real and sustainable annual growth following three consecutive years of robust funding increases that were significantly above the annual rate of biomedical inflation. Despite political and budgetary challenges, Congress has demonstrated an unwavering commitment to biomedical research by increasing the NIH budget by $7 billion, or 23 percent, since FY 2015. In addition to making medical research a national priority, both Congress and the administration have acknowledged the need for a strong FDA to ensure that research discoveries, once translated into therapies, are safe and effective, and reach the patients who need them as soon as possible.

We are at a pivotal moment in cancer research, and the positive funding momentum gained over the past three years must continue. During this time of both unprecedented scientific opportunity, and increasing incidence and associated mortality of cancer, the most valuable investments of federal dollars that Congress can make are in support of the medical research enterprise. This can most effectively be done through Congress providing robust, sustained, and predictable annual funding increases for the NIH. Annual increases in the NIH budget, coupled with consistent and sufficient funding for the FDA and the CDC in FY 2019 and beyond, will ensure the acceleration of the pace at which we make research discoveries and translate them into advances and population-based strategies that will save more lives from cancer.

We cannot continue to accelerate progress against cancer unless our elected leaders:

- **Continue to support robust, sustained, and predictable growth of the NIH budget** by providing an increase of at least $2 billion for NIH in FY 2019, for a total funding level of at least $39.1 billion.
- **Ensure that the $711 million in funding designated through the 21st Century Cures Act for targeted initiatives, including the National Cancer Moonshot, is fully appropriated in FY 2019 and is supplemental to the healthy increase for the NIH's base budget.**
- **Increase the FDA base budget in FY 2019 to $3.1 billion, a $308 million increase above its FY 2018 level,** to ensure support for regulatory science and to accelerate the pace of development of medical products that are safe and effective. Specifically, the AACR supports a funding level of $20 million for the FDA Oncology Center of Excellence in FY 2019.
- **Support the CDC Cancer Prevention and Control Programs with total funding of at least $517 million.** This includes funding for comprehensive cancer control, cancer registries, and screening and awareness programs for specific cancers.

By continuing to pursue an appropriations strategy that provides annual funding increases that are robust, sustained, and predictable for the NIH, NCI, FDA, and CDC, and by ensuring the funds available for the National Cancer Moonshot Initiative are fully appropriated in a way that supplements the NIH base budget, Congress can continue to help us transform cancer care, spur economic growth, and maintain our position as the global leader in science and medical research. Most importantly, it can help us save more lives from cancer.

A SNAPSHOT OF A YEAR OF PROGRESS

26%

REDUCTION IN U.S. CANCER DEATH RATE

1991

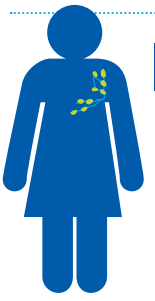
2015

2.4 million lives saved.

BETWEEN AUGUST 1, 2017, AND JULY 31, 2018, THE FDA APPROVED:

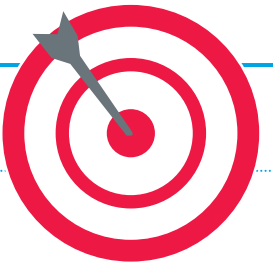
14 **new** anticancer therapeutics, which are bolstering the pillars of cancer care.

11 **previously approved** anticancer therapeutics for treating new types of cancer.



1 **new** surgery guiding system.

RESEARCH CONTINUES TO POWER PRECISION MEDICINE, LEADING TO:



The first therapeutic to target IDH2, which is benefiting patients with acute myeloid leukemia, like **Chuck Dandridge**, p. 68.

The first approval of a PARP inhibitor for treating patients with breast cancer, like **Lisa Quinn**, p. 76

A new androgen receptor-targeted therapeutic, which is allowing patients with prostate cancer like **Ron Scolamiero** to live metastasis free, p. 78.

RESEARCH CONTINUES TO ADVANCE IMMUNOTHERAPY, LEADING TO:

2 transformative new immunotherapeutics called CAR T-cell therapies, which are benefiting patients with certain blood cancers, like **Tori Lee** and **Mike Delia**, p. 84 and p. 86.

4 previously approved immunotherapeutics called checkpoint inhibitors, being approved for treating new types of cancer, including cervical, liver, and stomach cancers.

CANCER IN 2018

IN THIS SECTION, YOU WILL LEARN:

- In the United States, the age-adjusted overall cancer death rate has been decreasing since the 1990s, with the reduction from 1991 to 2015 translating into almost 2.4 million cancer deaths avoided.
- Not all segments of the U.S. population have benefited equally from advances against cancer.
- It is predicted that the number of new cancer cases diagnosed each year in the United States will increase in the coming decades, rising from 1.735 million in 2018 to 2.387 million in 2035.
- The cost of cancer is enormous, both in the United States and globally.

RESEARCH: DRIVING PROGRESS AGAINST CANCER

Research improves survival and quality of life for people around the world because it spurs the development of new and better ways to prevent, detect, diagnose, treat, and cure some of the many diseases we call cancer.

Every advance against cancer is the result of many years of hard work by individuals from all segments of the biomedical research community (see sidebar on **The Biomedical Research Community: Driving Progress Together**, p. 8).

Among the advances are the new anticancer therapeutics approved for use by the U.S. Food and Drug Administration (FDA). From August 1, 2017, to July 31, 2018, the FDA approved 14 new anticancer therapeutics (see **Table 1**, p. 9). During this period, the uses of 11 previously approved anticancer therapeutics were expanded by the FDA to include additional types of cancer.

Advances such as those listed in **Table 1** (see p. 9) are helping drive down U.S. cancer death rates and increase the number of children and adults who survive a cancer diagnosis (see **Figure 1**, p. 10) (2-4). In fact, the age-adjusted U.S. cancer death rate declined by 26 percent from 1991 to 2015, a reduction that translates into almost 2.4 million cancer deaths avoided (2). In addition, the U.S. 5-year relative survival rate for all cancers combined rose from 49 percent in the mid-1970s to 69 percent in 2014, which is the last year for which we have data (3).

The research that drives progress against cancer is made possible by investments from governments, philanthropic individuals and organizations, and the private sector the world over. In the United States, most federal investments in biomedical research are administered through the 27 institutes and centers of the National Institutes of Health (NIH). The largest of these institutes and centers is the National Cancer Institute (NCI), which is the federal government's principal agency for cancer research and training. Cancer research also is funded through the congressionally directed medical research program at the Department of Defense. For research investments to yield dividends in the form of new medical products and community-based programs to improve public health, we also need strong federal investment in agencies such as the FDA and the Centers for Disease Control and Prevention (CDC).

CANCER: AN ONGOING CHALLENGE

Although we have made incredible progress against cancer, this collection of diseases continues to be an enormous public health challenge worldwide (see sidebar on **Cancer: A Global Challenge**, p. 11). The magnitude of this challenge is illustrated by the fact that cancer accounted for 8.9 million or 16 percent of the 54.7 million deaths that occurred around the world in 2016, meaning that it accounted for one in every six deaths (5).

In the United States, cancer accounts for a greater proportion of deaths than it does worldwide. In 2016, it accounted for 598,038 of the 2.7 million deaths, which is 22 percent of deaths (9).

THE BIOMEDICAL RESEARCH COMMUNITY: DRIVING PROGRESS TOGETHER

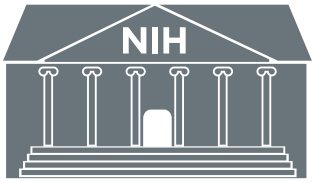
Progress against cancer occurs when individuals in different segments of the biomedical research community work together. Further increasing collaboration among stakeholders will accelerate the pace of lifesaving progress in the future. The stakeholders in the biomedical research community include:

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

policy makers;

health care providers;

federal funding organizations;



individual citizen advocates and members of advocacy groups;

biotechnology, pharmaceutical, diagnostics, and medical device companies;

philanthropic organizations and cancer-focused foundations;

regulators; and

academic and government researchers from a diverse array of specialties;

payers.

Adapted from (1)

TABLE 1

NEWLY FDA-APPROVED ANTICANCER THERAPEUTICS: AUGUST 1, 2017-JULY 31, 2018

Approved Indication	Generic Name	Trade Name	Formulation
CAR T-cell Therapy			
Certain type of non-Hodgkin lymphoma	axicabtagene ciloleucel	Yescarta	
Certain types of leukemia and non-Hodgkin lymphoma†	tisagenlecleucel	Kymriah	
Cell-cytoskeleton Modifying Agents			
Certain type of non-Hodgkin lymphoma†	brentuximab vedotin	Adcetris	
Cell-signaling Inhibitors			
Certain type of breast cancer	abemaciclib	Verzenio	
Certain type of non-Hodgkin lymphoma	acalabrutinib	Calquence	
Certain type of non-Hodgkin lymphoma	copanlisib	Aliqopa	
Certain type of thyriod cancer†	dabrafenib and trametinib	Tafinlar and Mekinist	+
Certain type of melanoma	encorafenib and binimetinib*	Braftovi and Mektovi	+
Certain type of blood cancer†	vemurafenib	Zelboraf	
DNA-damaging Agents			
Certain types of leukemia	daunorubicin and cytarabine	Vyxeos	
Certain types of leukemia	inotuzumab ozogamicin	Besponza	
Certain type of leukemia†	gemtuzumab ozogamicin	Mylotarg	
DNA-repair Inhibitors			
Certain breast cancers†	olaparib*	Lynparza	
Epigenome-modifying Agents			
Certain type of leukemia	enasidenib*	Idhifa	
Certain type of leukemia	ivosidenib*	Tibsovo	
Hormones/Antihormones			
Prostate cancer	apalutamide	Erleada	
Immune-checkpoint Inhibitors			
Certain type of lung cancer†	durvalumab	Imfinzi	
Certain types of colorectal† and liver cancer†	nivolumab	Opdivo	
Certain types of colorectal and kidney cancer†	nivolumab and ipilimumab	Opdivo and Yervoy	+
Certain types of lymphoma, stomach, and cervical cancer†	pembrolizumab*	Keytruda	
Radiation-emitting Therapeutics			
Certain types of neuroendocrine tumors	lutetium 177 dotatate	Lutathera	
Certain types of neuroendocrine tumors	iobenguane I 131	Azedra	

†new cancer type approved 2017–2018

* requires a companion diagnostic

Where multiple trade names are used, only the most common have been listed

Variable Progress Between Types of Cancer and Stages of Diagnosis

Among the challenges we face is that the advances we have made have not been uniform for all types of cancer. For example, while death rates for the four most commonly diagnosed cancers in the United States—breast, colorectal, lung, and prostate cancer—have been declining for more than a decade, those for other forms of cancer—most notably brain, liver, and uterine cancer—have been increasing in recent years (2).

In addition, advances have not been uniform for all stages of a given type of cancer. 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 (10).

Given these challenges, 5-year relative survival rates for U.S. patients vary widely depending on both the type of cancer diagnosed and the stage at diagnosis (2, 10).

Disparities in Progress for Distinct Population Groups

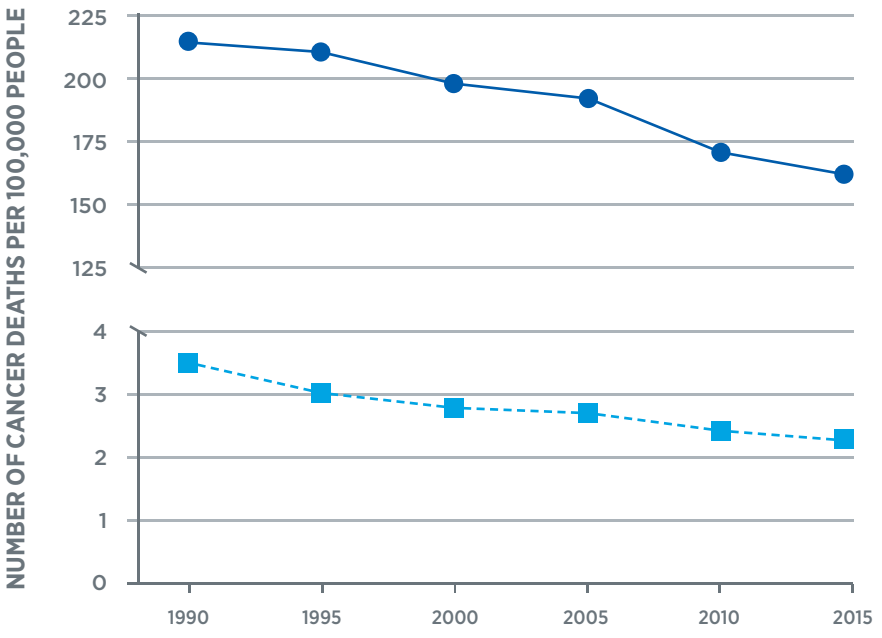
Cancer health disparities pose another pressing challenge both globally and nationally.

The 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 treatment, burden of cancer or related health conditions, screening rates, and stage at diagnosis that exist among certain segments of the population (11) (see sidebar on **What Are Cancer Health Disparities?**, p. 12 and the sidebar on **U.S. Cancer Health Disparities**, p. 14).

There are many complex and interrelated factors that contribute to U.S. cancer health disparities, which makes it difficult to isolate and study the relative contribution of each (see sidebar on **Why Do Cancer Health Disparities Exist?** p. 13). However, given that a significant proportion of the U.S. population falls into one or more risk categories, it is important that research into these specific issues continues.

FIGURE 1

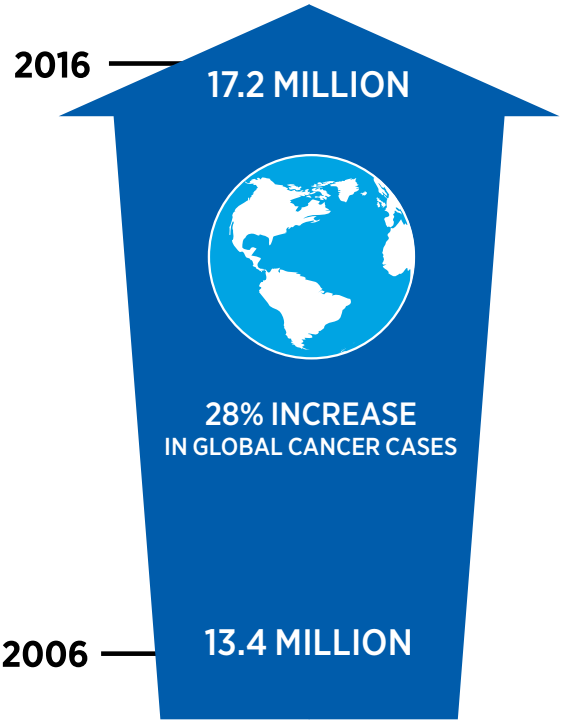
MAKING PROGRESS AGAINST CANCER

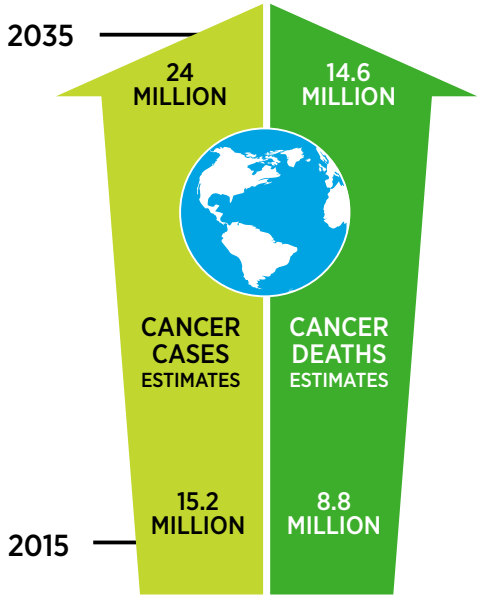


The age-adjusted overall U.S. cancer death rates for adults (—●—), and children and adolescents (ages 0 to 19) (- -■- -) have been declining steadily since the early 1990s. In 1990, there were 214.95 cancer deaths per 100,000 U.S. adults. By 2015, the most recent year for which these data are available, this had dropped to 158.68 per 100,000, a decline of 26 percent. During this period, the number of deaths from childhood cancer dropped from 3.4 per 100,000 U.S. children and adolescents to 2.3 per 100,000, a drop of 32 percent (3).

CANCER: A GLOBAL CHALLENGE

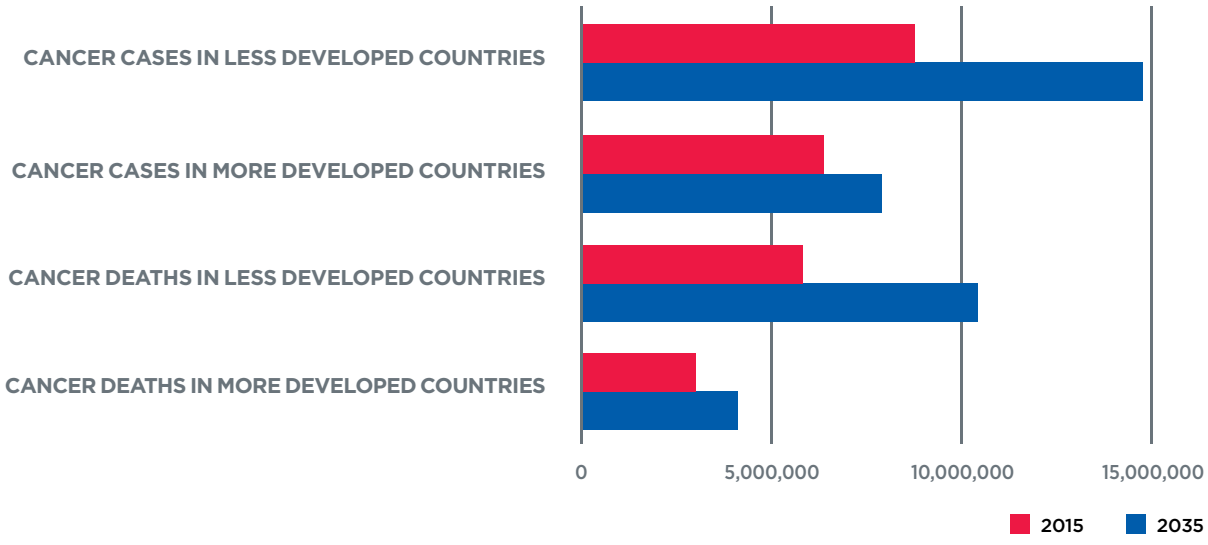
Globally, the number of cancer cases has been steadily rising for many years (6).





The number of cancer cases and the number of cancer deaths are expected to increase significantly in the coming decades if new and more effective approaches to cancer prevention, early detection, and treatment are not developed and effectively implemented (7).

The burden of cancer is expected to grow most in less developed regions of the world (7).



Given the growing global burden of cancer, it is imperative that the biomedical research community work together to drive down cancer incidence and mortality. One area in which progress is urgently needed is the establishment of population-based cancer registries in all countries because the collection of high-quality cancer surveillance data is essential for developing effective national cancer control plans. Currently, only one in five low- and middle-income countries has the necessary data to drive policy and reduce the burden and suffering caused by cancer, according to the International Agency for Research on Cancer (8).

WHAT ARE CANCER HEALTH DISPARITIES?

Cancer health disparities are defined by the National Cancer Institute 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 treatment, burden of cancer or related health conditions, screening rates, and stage at diagnosis that exist among certain segments of the population (11), including:

racial and ethnic minority groups;

individuals of different ancestry;

individuals of low socioeconomic status;

individuals who lack or have limited health insurance coverage;

residents in certain geographic locations, including rural areas;

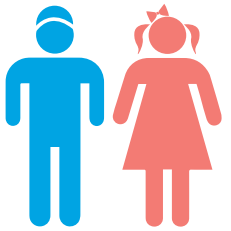
immigrants;

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

refugees or asylum seekers;

individuals with disabilities;

adolescents and young adults; and



the elderly.

Adapted from (1)

One area of intensive research investigation is furthering our understanding of the contribution of biological factors such as genetics to the adverse outcomes for certain U.S. populations. Only with new insights obtained through research and through the inclusion of all segments of the U.S. population in clinical trials will we develop and implement interventions that will eliminate cancer for all.

The Growing Cancer Burden

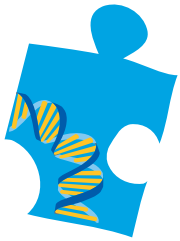
The public health challenge posed by cancer is predicted to grow considerably around the world in the coming decades unless we develop and effectively implement more effective strategies for cancer prevention, early detection, and treatment (see sidebar on **Cancer: A Global Challenge**, p. 11).

WHY DO CANCER HEALTH DISPARITIES EXIST?

Complex and interrelated factors contribute to U.S. cancer health disparities. The factors may include, but are not limited to, differences and/or inequalities in:

access to and use of health care;

genetics;



physical and mental health;

treatments received;

social and economic status;

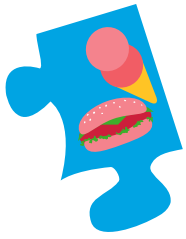
cultural beliefs;

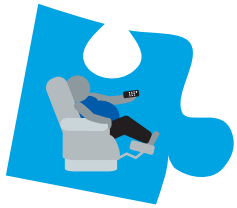
exposure to environmental cancer risk factors;

clinical trial participation;

health literacy; and

lifestyle, including weight, diet, and physical activity.





Adapted from (18)

U.S. CANCER HEALTH DISPARITIES

Significant progress has been made against cancer. However, not everyone has benefited equally from the advances and adverse differences in numerous cancer measures exist among certain segments of the U.S. population (see sidebar on **What Are Cancer Health Disparities?** p. 12). Some recently identified examples of disparities in cancer incidence rates, death rates, and stage at diagnosis 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. 26; **Disparities in Cancer Screening**, p. 47; **Disparities in Cancer Clinical Trial Participation**, p. 51; **Disparities in Treatment**, p. 57; and **Disparities in Quality of Life after a Cancer Diagnosis**, p. 96).

MORE THAN **DOUBLE**	Non-Hispanic black men have a prostate cancer death rate that is **more than double** that for men in any other racial or ethnic group (2).
75% AND 69% MORE LIKELY	African-American and Hispanic women are **75 percent and 69 percent**, respectively, **more likely** to be diagnosed with breast cancer at an advanced stage than non-Hispanic white women (12).
DOUBLE	Non-Hispanic black women have a triple-negative breast cancer incidence rate that is **double** that for non-Hispanic white women (13).
39% HIGHER	Non-Hispanic black women have a breast cancer death rate that is **39 percent higher** than that for non-Hispanic white women (13).
26% HIGHER	Men living in Appalachia have a lung cancer incidence rate that is **26 percent higher** than that for men living in the remainder of the United States (14).
61% AND 51% MORE LIKELY	Adolescents and young adults (ages 15 to 39) with head and neck cancer who have Medicaid coverage or no insurance are **61 percent and 51 percent**, respectively, **more likely** to die from their disease than those who have private insurance (15).
MORE THAN **20%** MORE LIKELY	Patients of low socioeconomic status with anal cancer are **more than 20 percent more likely** to die from the disease than those of high socioeconomic status (16).
3X MORE LIKELY	Women living with a same-sex relationship partner are **three times more likely** to die from breast cancer than women living with a male spouse or cohabiting relationship partner (17).

In the United States, it is predicted that 1,735,350 new cases of cancer will be diagnosed in 2018 and that 609,640 people will die from some type of the disease (10) (see **Table 2**, p. 16). These numbers are anticipated to rise significantly by 2035 (7). This is largely because cancer is primarily a disease of aging—53 percent of U.S. cancer diagnoses occur among those age 65 and older (3)—and this segment of the U.S. population is expected to grow from 52.5 million in 2018 to 78 million in 2035 (19). Also contributing to the projected increase in the number of U.S. cancer cases are continued use of cigarettes by 14 percent of U.S. adults (20) and high rates of obesity and physical inactivity, which are both linked to some common types of cancer (21).

Given the growing challenge presented by cancer, it is imperative that individuals from all segments of the biomedical research community work together to drive down cancer incidence and mortality.

CANCER: A COSTLY DISEASE. RESEARCH: A VITAL INVESTMENT

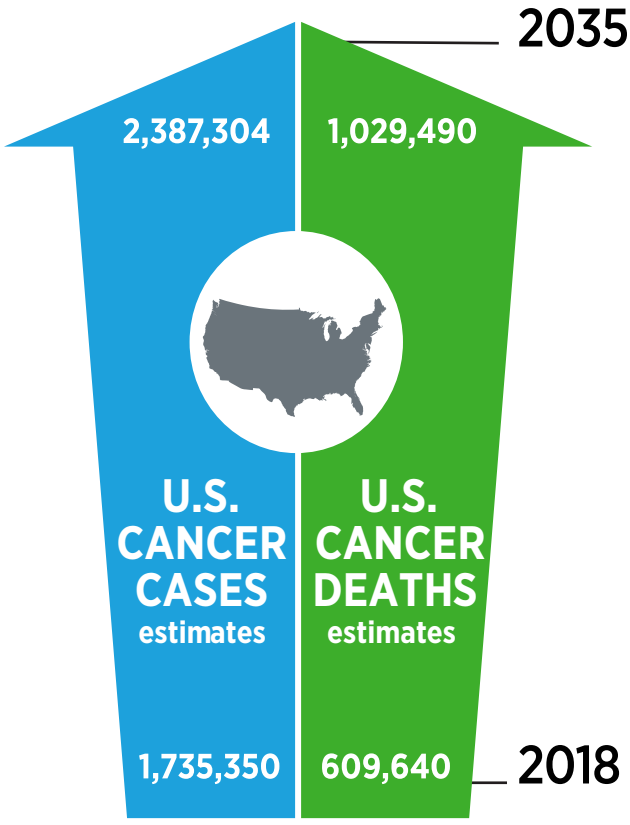
The immense global toll of cancer is felt through both the number of lives it affects each year and its economic impact. One study estimated that the direct costs related to the prevention and treatment of cancer, and the economic value of lives lost and disability caused, cost the world approximately $1.16 trillion in 2010 (22).

In the United States, the direct medical costs of cancer care are estimated to have been $80.2 billion in 2015, the most recent year for which these data are available (10). It is important to note that this number does not include the indirect costs of lost productivity due to cancer-related morbidity and mortality.

The costs of cancer care alone stand in stark contrast to the amount of money the federal government invests across all areas of biomedical research. In 2015, the same year that the direct medical costs of cancer care were $80.2 billion, the NIH budget was just $30.36 billion, of which $4.93 billion went to the NCI.

With the number of cancer cases projected to increase in the coming decades, we can be certain that both the direct and indirect costs will also escalate.

The rising personal and economic burden of cancer underscores the urgent need for more research so that we can accelerate the pace of progress against cancer. Recent advances, some of which are highlighted in this report, were made as a direct result of the cumulative efforts of researchers from across the spectrum of research disciplines. Much of their work, as well as the federal regulatory agency that assures the safety and efficacy of medical devices and therapeutic advances—the FDA—is supported by funds from the federal government. The consecutive multibillion dollar increases for the NIH budget in fiscal year (FY) 2016, FY 2017, and FY 2018 have helped to keep up with the pace of scientific innovation (see **Figure 19**, p. 109). It is imperative, however, that Congress continue to provide sustained, robust, and predictable increases in investments in the federal agencies that are vital for fueling progress against cancer, in particular the NIH, NCI, FDA, and CDC, in the years ahead (see **The AACR Call to Action**, p. 120).



Data from (7,10)

TABLE **2**

ESTIMATED INCIDENCE AND MORTALITY FOR SELECT CANCERS*

	ESTIMATED 2018 INCIDENCE			ESTIMATED 2018 DEATHS		
	Total	Male	Female	Total	Male	Female
All Sites	**1,735,350**	**856,370**	**878,980**	**609,640**	**323,630**	**286,010**
Head and Thorax Region						
Brain and other nervous system	23,880	13,720	10,160	16,830	9,490	7,340
Eye and orbit	3,540	2,130	1,410	350	190	160
Tongue	17,110	12,490	4,620	2,510	1,750	760
Mouth	13,580	7,980	5,600	2,650	1,770	880
Pharynx	17,590	14,250	3,340	3,230	2,480	750
Other oral cavity	3,260	2,440	820	1,640	1,280	360
Larynx	13,150	10,490	2,660	3,710	2,970	740
Lung & bronchus	234,030	121,680	112,350	154,050	83,550	70,500
Breast	268,670	2,550	266,120	41,400	480	40,920
Gastrointestinal System						
Esophagus	17,290	13,480	3,810	15,850	12,850	3,000
Stomach	26,240	16,520	9,720	10,800	6,510	4,290
Liver and intrahepatic bile duct	42,220	30,610	11,610	30,200	20,540	9,660
Gallbladder and other biliary	12,190	5,450	6,740	3,790	1,530	2,260
Pancreas	55,440	29,200	26,240	44,330	23,020	21,310
Small intestine	10,470	5,430	5,040	1,450	810	640
Colon and rectum	140,250	75,610	64,640	50,630	27,390	23,240
Anus, anal canal, and anorectum	8,580	2,960	5,620	1,160	480	680
Urogenital System						
Kidney and renal pelvis	65,340	42,680	22,660	14,970	10,010	4,960
Ovary	22,240		22,240	14,070		14,070
Uterine corpus	63,230		63,230	11,350		11,350
Uterine cervix	13,240		13,240	4,170		4,170
Urinary bladder	81,190	62,380	18,810	17,240	12,520	4,720
Prostate	164,690	164,690		29,430	29,430	
Testis	9,310	9,310		400	400	
Skin						
Skin (excluding basal and squamous)	99,550	60,350	39,200	13,460	9,070	4,390
Melanoma-skin	91,270	55,150	36,120	9,320	5,990	3,330
Hematological System						
Leukemia	60,300	35,030	25,270	24,370	14,270	10,100
Acute lymphocytic leukemia	5,960	3,290	2,670	1,470	830	640
Chronic lymphocytic leukemia	20,940	12,990	7,950	4,510	2,790	1,720
Acute myeloid leukemia	19,520	10,380	9,140	10,670	6,180	4,490
Chronic myeloid leukemia	8,430	4,980	3,450	1,090	620	470
Lymphoma	83,180	46,570	36,610	20,960	12,130	8,830
Hodgkin lymphoma	8,500	4,840	3,660	1,050	620	430
Non-Hodgkin lymphoma	74,680	41,730	32,950	19,910	11,510	8,400
Myeloma	30,770	16,400	14,370	12,770	6,830	5,940
Other Cancers						
Bones and joints	3,450	1,940	1,510	1,590	930	660
Soft tissue (including heart)	13,040	7,370	5,670	5,150	2,770	2,380

* Rounded to the nearest 10; estimated new cases exclude basal cell and squamous cell skin cancers and in situ carcinomas except urinary bladder. About 63,960 cases of carcinoma in situ of the female breast and 87,290 cases of melanoma in situ will be newly diagnosed in 2018.

Source: Estimated new cases are based on cancer incidence rates from 49 states and the District of Columbia during 2000-2014 as reported by the North American Association of Central Cancer Registries, representing about 98% of the U.S. population. Estimated deaths are based on U.S. mortality data during 2001-2015, National Center for Health Statistics, Centers for Disease Control and Prevention.

UNDERSTANDING CANCER DEVELOPMENT

IN THIS SECTION, YOU WILL LEARN:

- Research provides our understanding of the biology of cancer, including its initiation, development, and progression.
- Cancer is not one disease; it is a collection of diseases characterized by the uncontrolled growth of cells.
- Changes in the genetic information in a normal cell lead to cancer initiation and development in most cases.
- A cancer cell's surroundings influence disease development and progression.
- The most advanced stage of cancer, metastatic disease, accounts for most deaths from cancer.
- The more we know about the interplay among the individual factors influencing cancer biology, the more precisely and effectively we can prevent and treat cancer.

Discoveries across the breadth of biomedical research, from basic science to translational and clinical research and population research, have led to our current understanding of how cancer arises and develops (see sidebar on **What Is Basic Research and How Does It Drive Progress Against Cancer?** p. 18).

We have learned that cancer is a collection of diseases that arise due to uncontrolled cell multiplication. In adults, cell multiplication is a highly controlled process that occurs mostly to replenish cells that die due to normal wear and tear or damage from external factors. If the processes that control normal cell multiplication and lifespan go awry, cells start multiplying uncontrollably, fail to die when they should, and begin to accumulate. In body organs and tissues, the accumulating cells form masses called tumors, whereas in the blood or bone marrow they crowd out normal cells. Over time, some cancer cells invade local and distant tissues, a process termed metastasis, by entering the bloodstream or lymphatic network, and form secondary tumors at remote sites. Most deaths from cancer are due to metastasis.

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) units arranged in a particular order and packaged into condensed structures called chromosomes, inside the cell's nucleus (see sidebar on **Genetic and Epigenetic Control of Cell Function**, p. 18). The order of the DNA units as well as its three-dimensional structure dictates which protein and how much of it is made by each cell.

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. 19). Each person's cancer has a unique combination of mutations, and as a cancer progresses, additional mutations accumulate. The number of cells within a growing tumor that carry a given mutation depends on when the mutation was acquired during tumor growth. Thus, even within the same tumor, different cancer cells often have different genetic mutations. This variation, or heterogeneity, within a tumor or between a primary and metastatic tumor, is a leading cause of resistance to treatment and thereby disease progression.

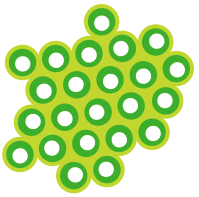
Although 5 to 10 percent of cancer-causing mutations can be inherited (see **Table 3**, p. 20), most are acquired over an individual's lifetime due to errors arising during normal cell multiplication or because of environmental exposures, lifestyle factors, or coexisting health conditions that fuel chronic inflammation (see sidebar on **Sources of**

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

The National Institutes of Health (NIH) defines basic research (also referred to as basic science 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. NIH-funded basic research projects significantly contribute to novel target identification and drug development (23, 24).

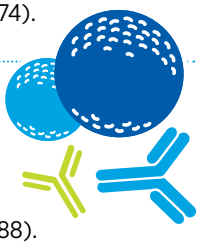
Discovery of **DNA and its 3-dimensional structure** paved the way for understanding **genetic mutations**, the underlying basis of most cancers.

Understanding the basic molecular biology of **DNA replication and cell division** led to the development of **chemotherapies** that kill rapidly dividing cancer cells.



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 and ovarian cancer treatment (see **Figure 14**, p. 74).

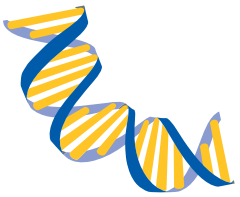
Decades of basic research in **immunology** led to the development of **immunotherapies** that have revolutionized the field of cancer treatment (see **Figure 16**, p. 88).

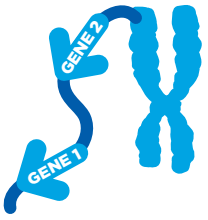


Basic research into the immune system of bacteria led to the development of **CRISPR technology**, and its utility to treat cancer is being investigated.

GENETIC AND EPIGENETIC CONTROL OF CELL FUNCTION

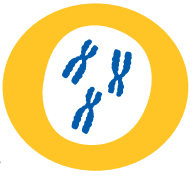
The genetic material of a cell comprises strings of four **deoxyribonucleic acid (DNA)** units called bases.





DNA bases are organized into **genes**. The order, or sequence, of the bases provides the code read by the cell to produce the various proteins it 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 chemical marks, called **epigenetic marks**, on the DNA and histones together determine whether a gene is accessible for reading. The sum of these chemical 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)

Genetic Mutations, p. 21). Ongoing research continues to uncover the mutational landscape of specific cancer types (25). For example, scientists have recently discovered that several childhood cancers carry fewer single base changes, but more copy number variations and/or structural rearrangements, than the same cancer in adults (26, 27).

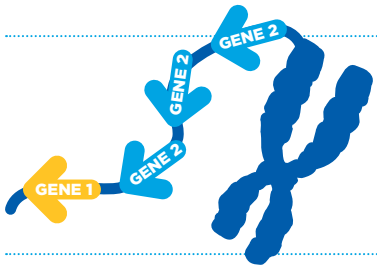
Not all mutations acquired by a cell lead to cancer. In fact, the identity of mutations and the order and speed at which a cell acquires them determine whether a cancer will develop and, if a cancer does develop, the length of time it takes to happen. The progressive nature of cancer provides distinct sites for medical intervention to prevent cancer, detect it

GENETIC MUTATIONS

The types of genetic mutation known to lead to cancer include:

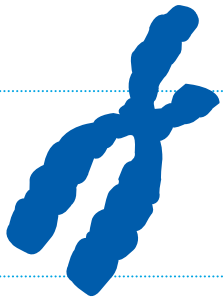
Single base changes

- Some mutations can lead to the generation of altered versions of normal proteins, and these may cause cancer to develop.
- Deletion or insertion of a single base can result in new proteins or loss of protein function, which can lead to cancer.



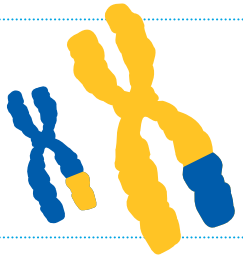
Extra copies of genes (gene amplification)

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



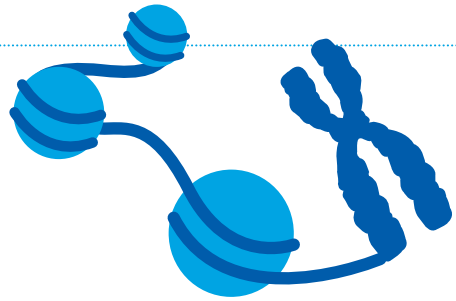
Large deletions

Loss of DNA can result in loss of genes necessary to stop or control the growth of cancer.



Genetic recombination

Exchange of DNA across different parts of the genome can lead to entirely new proteins that can drive the development of cancer.



Mutations that alter the epigenome

Several proteins read, write, or erase the epigenetic marks on DNA or the histones around which it is packaged. Mutations in the genes that produce these proteins can lead to cancer.

Of note, genetic mutations do not always result in cancer.

Adapted from (1)

TABLE **3**

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 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's anemia and telomere syndromes	*FANCC, FANC, FANCB, FANCS, 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 cancers, pituitary adenomas, and 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

early, or treat progressive disease. In general, the further a cancer has progressed, the harder it is to stop the chain of events that leads to the emergence of metastatic disease, which is the cause of most deaths from solid tumors (see **Screening for Early Detection**, p. 38).

In addition to genetic mutations, changes in the physical structure of DNA caused by modification of the DNA and the proteins associated with it, termed epigenetic modifications, are frequently detected in cancer cells (see sidebar on **Genetic and Epigenetic Control of Cell Function**, p. 18). Epigenetic modifications regulate how and when our genes are turned "on" or "off" and can be made by specialized proteins that "add" or "erase" unique chemical modifications on DNA and/or histones (32). In contrast to genetic mutations, epigenetic changes are often reversible, providing an attractive opportunity for therapeutic intervention. Our understanding of the role of epigenetics in cancer is, however, still incomplete, and further research is needed to reveal the real therapeutic potential of the cancer epigenome.

CANCER DEVELOPMENT: INFLUENCES OUTSIDE THE CELL

Cancer is primarily caused by the disruption of normal cellular functions through genetic and epigenetic changes. Once a tumor is initiated, however, complex interactions between cancer cells and their surrounding environment—known as the tumor microenvironment—can contribute to disease progression.

The tumor microenvironment is a specialized niche surrounding the cancer cells (see sidebar on **Cancer Growth: Local and Global Influences**, p. 22). Bidirectional communication between cancer cells and the tumor microenvironment affects cell multiplication, tumor heterogeneity, and tumor metastasis (33, 34). Furthermore, the tumor microenvironment can shelter cancer cells from the effects of radiation, chemotherapy, and immunotherapy, thereby rendering them resistant to treatment (35). Future studies are likely to identify additional cellular and molecular mechanisms by which the tumor microenvironment interacts with cancer cells and may help us develop new and improved therapeutics.

CANCER DEVELOPMENT: INTEGRATING OUR KNOWLEDGE

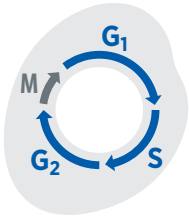
Knowledge is our greatest strength in driving progress against cancer. Knowing why a cancer develops will help us determine how to treat it. Comprehensive analyses of

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:

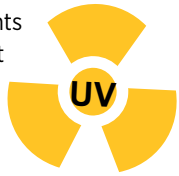
Five to 10 percent of all new U.S. cancer cases are linked to inherited genetic mutations, which are present in each cell of the body from birth (28, 29).

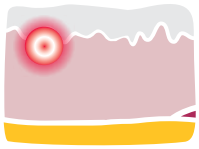
Most mutations, however, are acquired during a person's lifetime.



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

- Some occur because of exposure to factors that damage genetic material, such as toxicants in tobacco smoke and ultraviolet (UV) light from the sun (see **Figure 3**, p. 25).





- Yet others occur as a result of chronic inflammation fueled by medical conditions such as Crohn's disease [as reviewed in (30)].

These factors come together to determine the chance that an individual cell has of acquiring mutations over time. This, in turn, helps determine the overall risk that a person will develop a particular type of cancer, although it is important to note that not all mutations lead to cancer.

Adapted from (31)

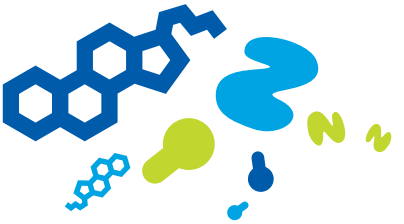
CANCER GROWTH: LOCAL AND GLOBAL INFLUENCES

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 normal parts of the tissue in which the cancer is growing, systemic factors that transiently percolate through the tissue, and cells that are actively recruited to the tissue.

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).

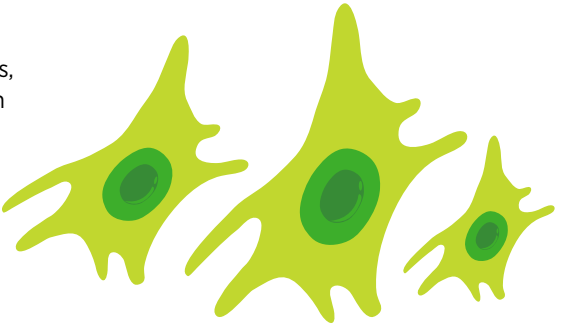
The **matrix** of proteins that surrounds the cancer cells can influence cancer formation, metastasis, and other processes.

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



The **immune system** can identify and eliminate cancer cells, although in many cases this 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.

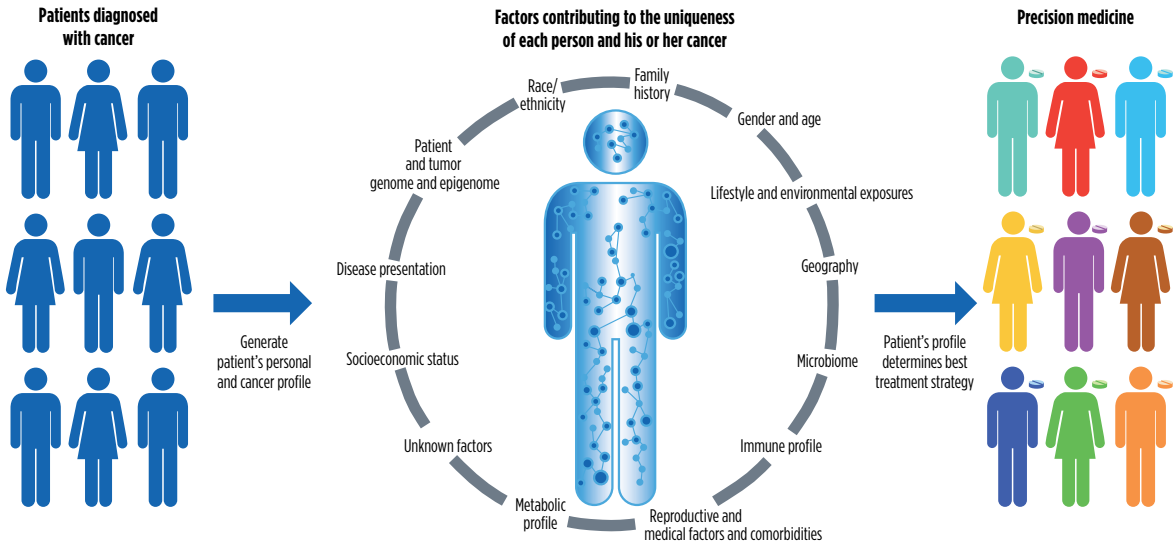
Other tissue-specific **tumor-associated cells**, such as pericytes, fibroblasts, and astrocytes, can support tumor growth through various mechanisms including stimulating tumor growth, triggering formation of new blood vessels, and enhancing survival of cancer cells.



Adapted from (36)

FIGURE 2

PRECISION MEDICINE



Precision medicine, sometimes referred to as personalized medicine, is broadly defined as treating patients based on characteristics that distinguish them from other patients with the same disease. The factors that contribute to the uniqueness of each person and his or her cancer include, but are not limited to, a person's genome, the genome and epigenome of his or her cancer, disease presentation, gender, exposures, lifestyle, microbiome, comorbidities, and other yet-to-be-discovered features. Currently, genomics is the predominant factor influencing precision medicine in oncology, but as we learn more about additional factors we can create a more personalized profile for each patient. The figure highlights how factors that influence precision medicine can be utilized to stratify a group of patients with a site-specific cancer. Development of a personalized profile for each patient has the potential to allow physicians to tailor treatment for each patient.

human cancer genomes over the past decade have revealed numerous genetic mutations that are associated with a variety of cancers (37, 38). These discoveries led to the development of a series of therapeutics targeted to rectifying the cellular changes that arise due to the mutations.

We have also learned that each person's cancer is unique, in part, because it is influenced by a patient's biological characteristics and lifestyle factors. As a result, we have seen a major shift in treatment from a "one size fits all" to a more personalized approach. Precision medicine aims to tailor each person's health care to the prevention and/or treatment strategies most likely to be of benefit, sparing each person the cost of and potential harms from prevention interventions and/or treatments that are unlikely to benefit him or her (see **Figure 2**).

Over the past decade, we have made significant progress in how we understand and treat the complex group of diseases we call cancer. Nevertheless, our current knowledge of cancer-causing genetic, lifestyle, and environmental risks is incomplete, and ongoing research will continue to uncover additional cellular and molecular alterations that lead to cancer development. An area of primary focus is understanding the biological basis for disparities in cancer incidence and outcomes among certain segments of the U.S. population (see sidebar on **U.S. Cancer Health Disparities**, p. 14). Concerted efforts are needed from all sectors of the biomedical research community to ensure that the new wave of scientific discoveries benefits the entire population.

PREVENTING CANCER: IDENTIFYING RISK FACTORS

IN THIS SECTION, YOU WILL LEARN:

- In the United States, 4 out of 10 cancer cases and almost half of all deaths from cancer are associated with preventable risk factors.
- Not using tobacco is one of the most effective ways a person can prevent cancer from developing.
- Nearly 20 percent of U.S. cancer diagnoses are related to excess body weight, alcohol intake, poor diet, and physical inactivity.
- Many cases of skin cancer could be prevented by protecting the skin from ultraviolet radiation from the sun and indoor tanning devices.
- Nearly all cases of cervical cancer could be prevented by HPV vaccination, but most U.S. adolescents have not received the recommended doses of the vaccine.
- There are disparities in the burden of cancer attributable to preventable causes among certain segments of the U.S. population.

Decades of basic, epidemiologic, and clinical research have led to the identification of several factors that increase a person's chance of developing cancer (see **Figure 3**, p. 25). These factors, which are known as cancer risk factors, can alter the genetic or epigenetic information in a person's cells. This may directly lead to cancer development or increase the person's chance of developing cancer later in life. Many cancer risk factors, such as smoking, are also associated with worse outcomes after a cancer diagnosis (see **Modifying Behaviors to Improve Outcomes**, p. 97).

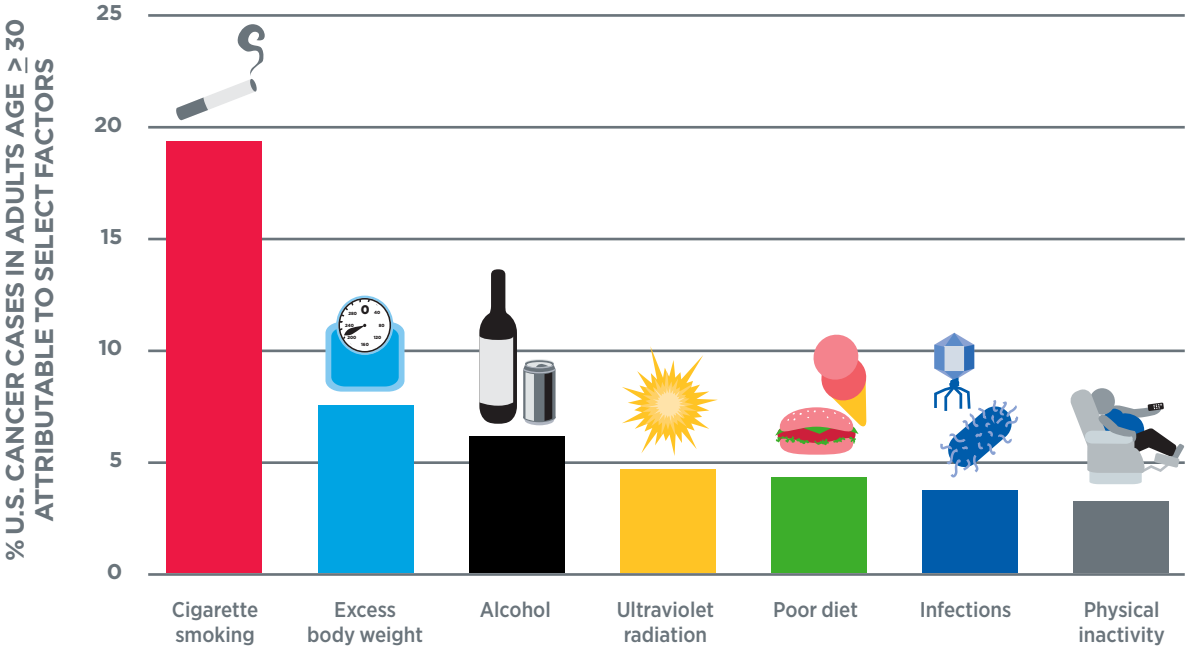
Researchers estimate that more than 40 percent of the cancer cases diagnosed in the United States in 2014 and nearly half of all deaths from cancer were caused by potentially avoidable cancer risk factors, including tobacco use, poor diet, alcohol intake, physical inactivity, and obesity (21). In addition, vaccination against infection with the human papillomavirus (HPV) and decreasing exposure to ultraviolet (UV) radiation from the sun and indoor tanning devices can further reduce the burden of certain types of cancer (40).

Many cancer risk factors are also risk factors for 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, a recent study showed that adherence to a low-risk lifestyle, such as never smoking, eating healthily, staying active, and limiting alcohol consumption can increase life expectancy by more than a decade (41).

A critical issue hindering improvements in public health is our inability to effectively communicate the current knowledge on avoidable cancer risk factors to the general population and implement interventions to minimize these risks. In fact, according to a recent report, most U.S. adults are still unaware of the significant cancer risks associated with obesity and alcohol use (42). This emphasizes the continued need for widespread dissemination of our current knowledge of these cancer risk factors, as well as the implementation of known preventive strategies to reduce risky behaviors in all population groups. In addition to health benefits, effective implementation of preventive measures may also lead to significant economic savings over time. Targeted efforts are also important since certain segments of the U.S. population, such as racial and ethnic minorities, and individuals of lower socioeconomic status, are disproportionately exposed to many of the potentially avoidable risk factors (see sidebar on **Disparities in the Burden of Avoidable Cancer Risk Factors**, p. 26).

FIGURE 3

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 (21).

ELIMINATE TOBACCO USE

Tobacco use is the leading preventable cause of cancer and deaths from cancer. It causes cancer because tobacco or secondhand smoke exposes individuals to many harmful chemicals that damage DNA, causing genetic and epigenetic alterations that lead to cancer development (48-50).

Smoking is linked to 17 different types of cancers in addition to lung cancer (see **Figure 4**, p. 27), and in 2014, which is the most recent year for which data are available, it caused about 169,180 deaths from cancer (51, 21). Even individuals who smoke fewer than one cigarette per day over their lifetime have a higher risk of death than nonsmokers. Fortunately, cessation at any age can reduce the risk of cancer occurrence and death from the disease (52, 53). Thus, one of the most effective ways a person can lower his or her risk of developing cancer and lower his or her risk of other smoking-related conditions such as cardiovascular, metabolic, and lung diseases, is to avoid or eliminate tobacco use.

Implementation of major public education and policy initiatives has significantly lowered cigarette smoking rates in the United States; the number of adult cigarette smokers dropped from 21 percent in 2005 to 14 percent in 2017 (20). The proportion of U.S. adult ever-smokers who quit smoking also significantly increased during the same period (54). Despite these trends, more than 37 million adults were still smoking in 2016 (54). There are striking sociodemographic disparities in smoking behavior (see sidebar on **Disparities in the Burden of Avoidable Cancer Risk Factors**, p. 26). Thus, it is imperative that researchers, advocates, and policy makers continue to work together to develop and implement population-based interventions that have been shown to decrease smoking and lung cancer rates such as tobacco price increases, public campaigns, and smoke-free laws to reduce smoking and related cancer burden in the United States (see sidebar on **Highlighting the New Corrective Advertisements**, p. 118) (55). Moreover, we need to use current tobacco-cessation strategies more widely because nicotine replacement therapy, use of prescription medications (e.g., buproprion

and varenicline), and counseling have all been shown to be effective in enhancing the chances of long-term abstinence from smoking (56).

The use of other combustible tobacco products, such as cigars, smokeless tobacco products (e.g., chewing tobacco and snuff), and water pipes, are also associated with cancer (57). Electronic cigarettes (e-cigarettes) are a rapidly emerging tobacco product. With more than 2 million middle- and high-school students reporting using e-cigarettes in 2017 (58), their use among U.S. youth is a major public health concern (see sidebar on **E-Cigarettes: What Have We Learned and What Do We Need to Know?** p. 28) (59, 60). A major appeal of e-cigarettes is the flavorings used in the e-liquids, which are often labelled as kid-friendly food products, such as juice, candy, or cookies (61). E-cigarette advertising is associated with higher use among youth (62). Therefore, it is concerning that nearly 80 percent of middle- and high-school students in the U.S. were exposed to e-cigarette advertisements in 2016 (63). Effective strategies to curb youth access to e-cigarettes and their exposure to e-cigarette advertising need to be developed and implemented.

More research is needed to understand the long-term health risks of e-cigarettes as well as their effectiveness in smoking cessation (59). Based on current evidence the value of e-cigarettes in smoking cessation is equivocal (65-67). However, there is strong evidence that the use of e-cigarettes may act as a gateway to smoking in youth (61, 68). Therefore, researchers, clinicians, advocates, and policy makers must continue to work together to educate

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:

4X LESS LIKELY

College-educated individuals are nearly **4 times less likely** to smoke than those with a high-school education or less (43).

2X

Among individuals with bipolar disorder or schizophrenia, smoking rates are **twice** what they are among the general population (43).

MORE THAN 2X

Non-Hispanic black individuals are **more than twice as likely** to be exposed to secondhand smoke compared to non-Hispanic whites (44).

LIKELY

Non-Hispanic black women are **most likely** (49%) to be obese compared with Hispanic women (34%) and non-Hispanic white women (29%) (20).

HIGHER

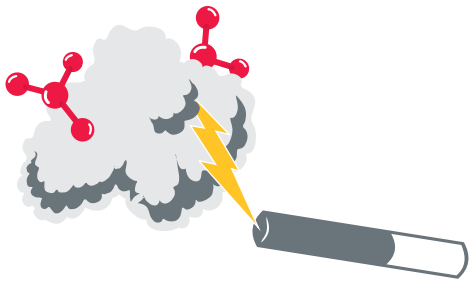
The age-adjusted rate of overweight- and obesity-related cancers is higher among black (134.2) and American Indian/Alaska Native males (121.9) compared with white males (114.2) (45).

HIGHER

American Indians/Alaska Natives have a higher prevalence (27.7%) of binge drinking compared with white (23.5%) or Asian Americans (14.5%) (46).

HIGHER

Adolescents living in metropolitan areas have a higher HPV vaccination uptake (65.9%) compared with those in nonmetropolitan areas (50.4%) (47).

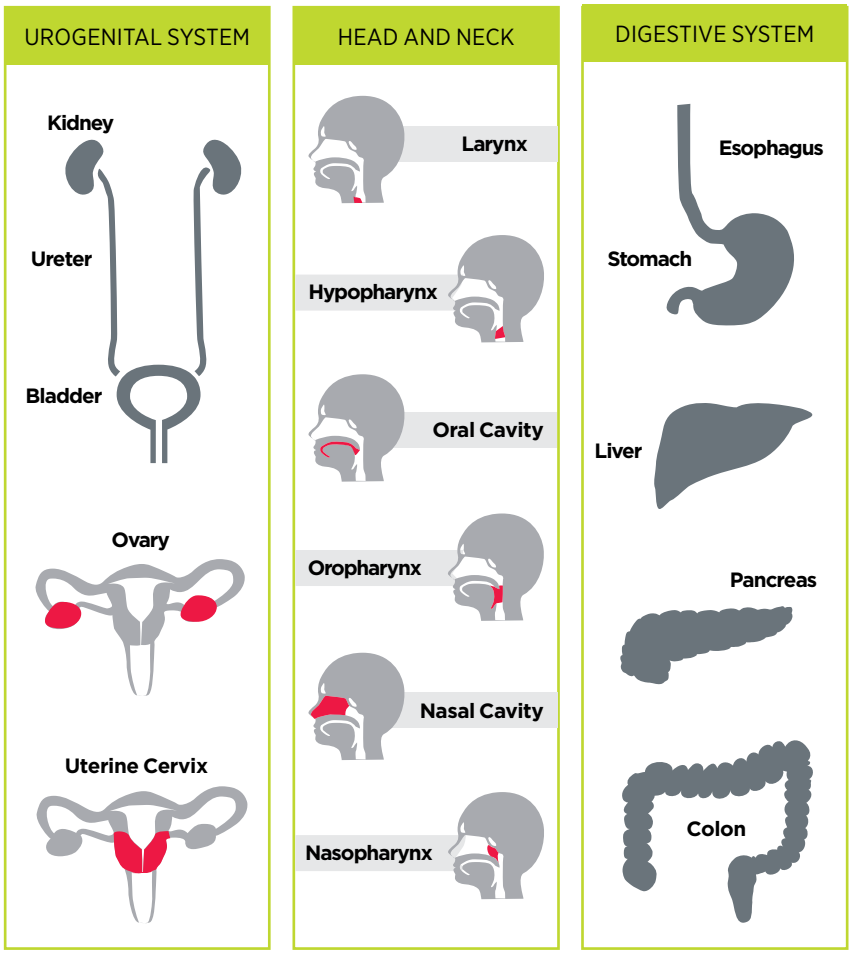


Adolescent use of e-cigarettes can expose users to **toxicants that increase the risk of DNA damage** (64).

Individuals living in communities with smoke-free laws were **8 percent less likely** than those living in communities without smoke-free protections to be diagnosed with lung cancer (55).

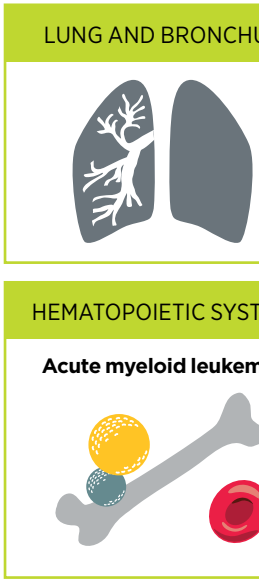
FIGURE **4**

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.

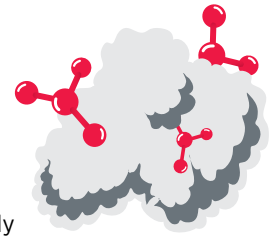
Adapted from (1).



E-CIGARETTES: WHAT HAVE WE LEARNED AND WHAT DO WE NEED TO KNOW?

E-cigarettes are battery-powered devices that can deliver nicotine and flavorings to the user in the form of an aerosol. The National Academy of Sciences, Engineering, and Medicine (NAS) issued a comprehensive report on the public health consequences of e-cigarettes in 2018 (61). The report offers insight on several aspects of e-cigarettes, including:

Constituents



- In addition to nicotine, they contain and emit many potentially toxic substances
- Exposure to nicotine is highly variable and depends on the characteristics of the device and e-liquids, and how the device is operated

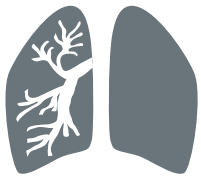
Use

- Highest among young adults
- Despite sharp increases between 2011 and 2015, recent data indicate possible stabilization of use

Role in smoking cessation and initiation

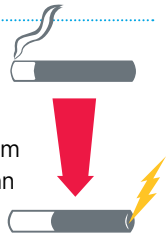
- More research is needed to evaluate their value as smoking cessation aids
- May increase youth transitioning to conventional cigarettes

Human health effects



- Need additional research to evaluate long-term health risks, including cancer, cardiovascular and pulmonary diseases, and pregnancy outcomes
- Use is more harmful than no tobacco use

Harm reduction compared to combustible tobacco



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

Safety

- 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 public about the health risks and identify best strategies to implement population-level regulations to reduce e-cigarette use among youth and young adults.

MAINTAIN A HEALTHY WEIGHT, EAT A HEALTHY DIET, AND STAY ACTIVE

Researchers estimate that 15 percent of all cancer cases diagnosed in the United States are related to people being overweight or obese, inactive, and/or eating a poor diet (21). Therefore, maintaining a healthy weight, being physically active, and consuming a balanced diet are effective ways a person can lower his or her risk of developing or dying from cancer (see sidebar on **Reduce Your Risk for Cancer Linked to Being Overweight or Obese, Being Inactive, and/or Consuming a Poor Diet**, p. 29).

Exactly how obesity increases a person's risk for cancer is not well understood, but accumulating evidence indicates a role for inflammatory immune cells in fat tissue (69).

Being overweight or obese as an adult increases a person's risk for 15 types of cancer (see **Figure 5**, p. 30) (72, 73). In 2014, overweight- and obesity-related cancers accounted for 40 percent of all cancer cases in the United States (45). Therefore, it is concerning that in the U.S., adult obesity rates nearly doubled over the past two decades, and only half of U.S. adults meet the recommended federal physical activity guidelines (see sidebar on **Physical Activity Guidelines**, p. 31) (20). These findings underscore the need for nationwide efforts to prevent and treat overweight and obesity.

The epidemic of obesity is directly related to an unbalanced energy intake. "Energy balance" refers to the difference

Eating a lot of **ultraprocessed foods** such as mass-produced desserts, sodas and sweetened drinks, processed meats, and snack foods is linked with increased cancer risk (71).

U.S. Preventive Services TASK FORCE

The U.S. Preventive Services Task Force (USPSTF), an independent, volunteer panel of national experts in prevention and evidence-based medicine, recommends screening all adults for obesity, and if applicable, for clinicians to offer or refer patients to behavior-based interventions for weight loss and weight loss maintenance.

between the number of calories consumed and the number burned. Tipping of this balance so that a person accumulates excess energy, which is stored in the body as fat, plays a crucial role in promoting obesity. While calories are consumed only through eating and drinking, they are burned in many ways. Simply existing, breathing, digesting food, and pumping blood around the body use some calories. Added to these expenditures are the calories burned through a person's daily routine; the more physical activity in a routine, the more calories are burned.

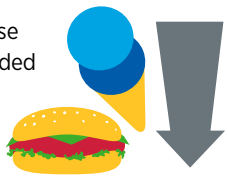
REDUCE YOUR RISK FOR CANCERS LINKED TO BEING OVERWEIGHT OR OBESE, BEING INACTIVE, AND/OR CONSUMING A POOR DIET

Research from the World Cancer Research Fund International shows that about one-fifth of all U.S. cancers and one-third of the most common types of cancer diagnosed in the United States are attributable to being overweight or obese, being inactive, and/or eating poorly. As such, among their recommendations are the following:

Be as lean as possible without becoming underweight, because 15 types of cancer have been causally linked to being obese or overweight (see **Figure 5**, p. 30).

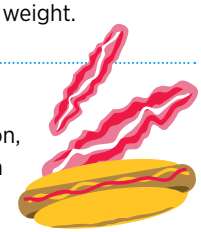
Be physically active for at least 30 minutes every day, because regular physical activity can decrease risk for certain cancers (see sidebar on **Physical Activity Guidelines**, p. 31).

Limit consumption of energy-dense foods (foods high in fats and/or added sugars and/or low in fiber) and avoid sugary drinks, because these contribute to weight gain.



Eat more of a variety of vegetables, fruits, whole grains, and beans, because these foods have a low energy density and, therefore, promote healthy weight.

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



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

Source: http://www.wcrf.org/int/research-we-fund/our-cancer-prevention-recommendations
Adapted from (31)

In the U.S.

more than
one in three adults
and
one in six children

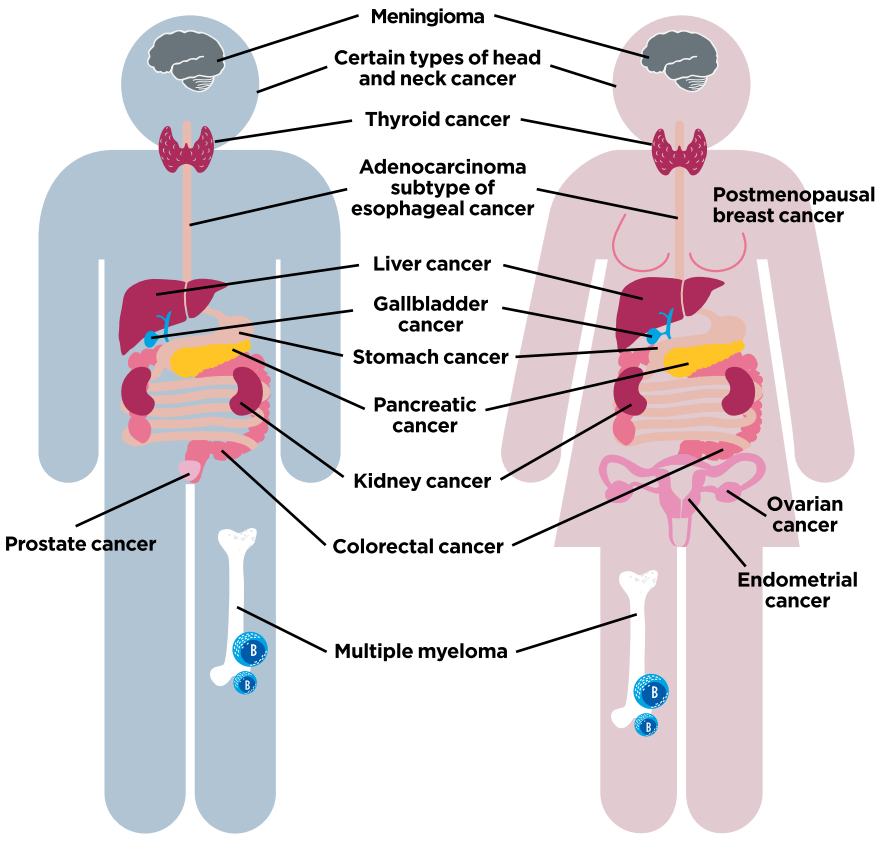
are currently obese (70).

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 (74). One recent policy initiative that is aimed at reducing obesity is the introduction of taxes on sugar-sweetened beverages, which is a major contributor of caloric intake among U.S. youth and adults, in seven local jurisdictions within the U.S. (75-77). Ongoing research is needed to evaluate the long-term effects of such policies on consumption, obesity, and obesity-related health outcomes.

Unfortunately, the burden of diet-related diseases, including cancer, is disparately higher in low-income communities (70). Low-income populations frequently live in "food deserts," which are neighborhoods lacking access to healthy food retail such as supermarkets, while having an overabundance of unhealthy and fast food options (70). Food deserts are associated with chronic conditions

FIGURE 5

WEIGHING THE EVIDENCE: CANCERS CAUSED BY OBESITY



Fifteen types of cancer—the adenocarcinoma subtype of esophageal cancer, certain types of head and neck cancer, advanced prostate cancer, meningioma, multiple myeloma, and colorectal, endometrial, gallbladder, kidney, liver, ovarian, pancreatic, stomach, thyroid, and postmenopausal breast cancers—have all been directly linked to being overweight or obese (72, 73).

Adapted from (31).

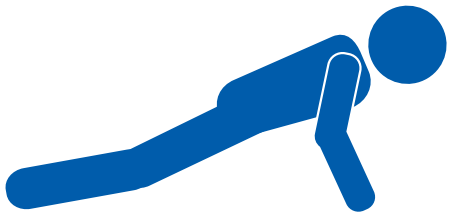
PHYSICAL ACTIVITY GUIDELINES

The U.S. Department of Health and Human Services recommends the following minimum physical activity levels to improve the nation's health; see http://www.health.gov/paguidelines/guidelines/summary.aspx.

For children and adolescents

Sixty minutes or more of physical activity such as running daily.

Muscle- and bone-strengthening exercises such as push-ups at least three days per week.

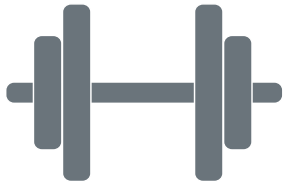


For adults

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.

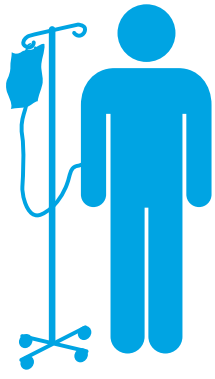
Moderate- or high-intensity muscle-strengthening activities two or more days per week.



For specific populations

Older adults, those who are pregnant, and/or those with disabilities should consult their physicians and the modified guidelines.

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



Adapted from (1)

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 (74): If alcohol is consumed, **it should be done in moderation and only by adults of legal drinking age.**

Moderate drinking:

≤ 1 drink per day for women and

≤ 2 drinks per day for men

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, is responsible for 88,000 deaths in the United States each year.

The U.S. Preventive Services Task Force (USPSTF) recommends that clinicians screen adults aged ≥18 years for alcohol misuse and provide persons engaged in excessive drinking with brief behavioral counseling interventions.

Alcohol consumption accounted for **245,000 deaths from liver cancer** globally in 2015 (88).

including obesity (78). The U.S. Department of Agriculture estimates that more than 23 million people live in low-income areas that are more than a mile (in the case of urban areas) or 10 miles (for rural areas) away from the nearest supermarket (70). These findings underscore the need for evidence-based health improvement strategies to increase access to affordable and nutritious food for all populations. Furthermore, educational interventions are essential to improve nutritional knowledge among low-income residents of food deserts, considering recent observations that the variation in access to supermarkets accounts for only a part of the difference in healthy eating between high- and low-income households (79). Also contributing to disparities in the burden of obesity-related diseases in low-income communities in urban areas is a lack of safe and affordable options for physical exercise, such as gyms, bike trails, and walking paths (70).

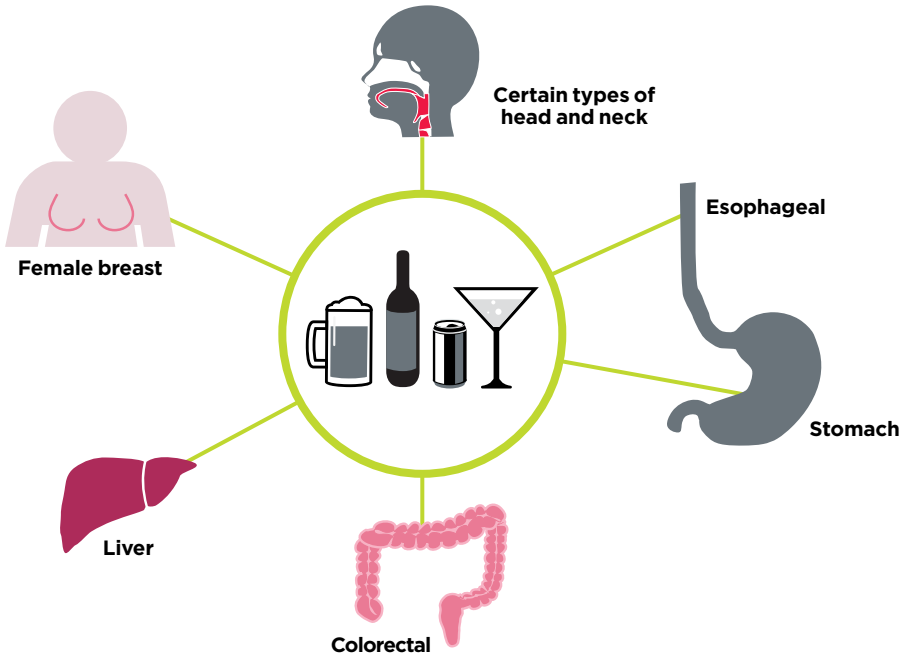
LIMIT ALCOHOL CONSUMPTION

Researchers estimate that alcohol consumption will be responsible for 5.6 percent of the new cancer cases diagnosed in the United States in 2018 and for 4 percent of the cancer deaths (21). Even modest use of alcohol may increase cancer risk, but the greatest risks are associated with excessive and/or long-term consumption (80-82) (see sidebar on **Guidelines for Alcohol Consumption**). Thus, it is concerning that in the United States, there has been a dramatic rise in high-risk alcohol consumption, with nearly 37 million adults reporting binge drinking, once a week, in 2015 (83, 84).

Alcohol consumption has been causally linked with six different types of cancers (see **Figure 6**, p. 33) (85). Researchers have identified multiple ways in which alcohol may increase the risk of cancer, including directly damaging

FIGURE 6

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 (85).

cellular DNA and proteins through the production of toxic chemicals, once alcohol is metabolized after drinking (86, 87).

Beyond the United States, alcohol poses a significant public health challenge globally, with a toll of more than 3 million deaths worldwide each year due to excessive use (86). These data underscore the importance of adherence to comprehensive guidelines, thus limiting alcohol intake (for those who drink) to 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.

PROTECT SKIN FROM UV EXPOSURE

Exposure to ultraviolet (UV) radiation from the sun or indoor tanning devices can cause genetic mutations and poses a serious threat for the development of all three main types of skin cancer—basal cell carcinoma, squamous cell carcinoma, and melanoma, which is the deadliest form of skin cancer. Thus, 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. 34).

In the U.S., melanoma incidence among non-Hispanic whites has increased in the past decade, particularly in individuals older than 55 years (89). To break the current trend by establishing skin cancer prevention as a national priority, the U.S. Surgeon General released A Call to Action report in 2014 (90). Since its release, multiple sectors including health care, government, business, advocacy, and communities have coordinated efforts and made major strides toward reducing risk exposure. As a result, indoor tanning among U.S. youth and adults has decreased significantly (91, 92). However, even in 2015, an estimated 7.8 adults and 1.2 million high school students engaged in indoor tanning and many reported experiencing sunburns (91, 92). Continued efforts from public health and medical communities are needed to further reduce the prevalence of indoor tanning and sunburn. Reducing indoor tanning has the potential to reduce melanoma incidence and mortality, as well as the economic costs related to skin cancers (93).

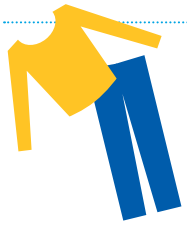
PREVENT INFECTION WITH CANCER-CAUSING PATHOGENS

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. 35). The most recent estimate is that 15 percent of all new cancer cases diagnosed worldwide in 2012 were attributable to persistent infection with pathogens, the most common

WAYS TO PROTECT YOUR SKIN

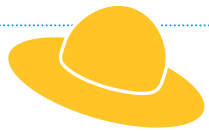
To reduce your risk of the three main types of skin cancer—basal cell carcinoma, squamous cell carcinoma, and melanoma—the Centers for Disease Control and Prevention recommends the following measures:

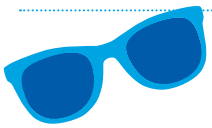
seek shade and limit time in the sun, especially during peak sun hours (10:00 a.m. to 4:00 p.m.);



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

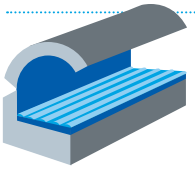
wear a wide-brimmed hat;





wear wrap-around sunglasses;

apply the recommended amount of a 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; and



avoid indoor tanning with UV devices like sunlamps, sunbeds, and tanning booths.

Adapted from (36)

of which were *Helicobacter pylori*, human papillomavirus (HPV), hepatitis B virus (HBV), and hepatitis C virus (HCV) (95). Thus, individuals can significantly lower their risks for certain types of cancer by protecting themselves from infection with cancer-associated pathogens 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. 36).

U.S. Preventive Services TASK FORCE

The U.S. Preventive Services Task Force 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 (94).

Although there are strategies available to eliminate, treat, or prevent infection with *Helicobacter pylori*, HBV, HCV, and HPV that can significantly lower an individual's risks for developing an infection-related cancer, it is important to note that these strategies are not effective at treating infection-related cancers once they develop. It is also clear that these strategies are not being used optimally. For example, even though the U.S. Preventive Services Task Force (USPSTF) recommended one-time HCV testing for baby boomers in 2013, data from a 2015 national survey showed that only 10.5 out of 76.2 million adults eligible for testing reported getting tested (96). Given that infection with HCV is estimated to be responsible for six out of 10 liver cancer cases diagnosed in the United States since 2000, the burden of this disease could be significantly reduced through more effective implementation of HCV screening and treatment (75, 95).

In the United States, an average of 38,793 HPV-associated cancers were diagnosed annually, from 2008 to 2012 (97). Research suggests that HPV vaccination could prevent nearly all cases of cervical cancer and many cases of oral and anal cancer. However, less than 50 percent of adolescents ages 13 – 17 years were up to date with the recommended HPV vaccination series in 2016 (47). This rate of uptake is much lower than occurs for other vaccinations received in adolescence (47). Thus, development of effective strategies to increase the uptake of HPV vaccines could have an immense impact on cancer prevention (see sidebar on **HPV Vaccination Recommendations**, p. 37). In this regard, one recent clinical trial showed an increase in vaccination rates when health care providers used a multicomponent intervention to facilitate communication with patients and their parents about the benefits of the HPV vaccine (98).

LIMIT EXPOSURE TO ENVIRONMENTAL RISK FACTORS

Environmental exposures to pollutants and 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 (102). Other examples of environmental cancer risk factors include asbestos, lead, radiation, and benzene. According to the World Health Organization, 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 many environmental cancer risk factors, 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 the individual'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. A recent study from the U.S. Environmental Protection Agency (EPA) evaluated the environmental quality index, a measure of overall environmental exposures, and found a potential increase in overall cancer incidence with decreasing environmental quality (103).

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. For example,

TABLE 4 **CANCER-CAUSING PATHOGENS**

Bacteria

Infectious Agent	Cancer	% of global cancer cases attributable to infection*
Helicobacter pylori	Stomach cancers	32.5

Parasites

Infectious Agent	Cancer	% of global cancer cases attributable to infection*
Clonorchis sinensis	Biliary, gallbladder, and pancreatic cancers	0.1
Opisthorchis viverrini	Biliary, gallbladder, and pancreatic cancers	
Schistosoma haematobium	Bladder cancer	0.3

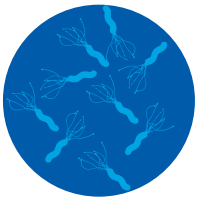
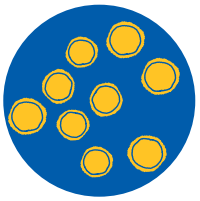
Viruses

Infectious Agent	Cancer	% of global cancer cases attributable to infection*
Epstein-Barr virus (EBV)	Hodgkin and certain non-Hodgkin lymphoma, and stomach and nasopharyngeal cancers	5.4
Hepatitis B/C viruses (HBV and HCV)	Hepatocellular carcinoma	29.5
Human herpes virus type-8 (HHV-8; also known as Kaposi sarcoma herpes virus)	Kaposi sarcoma and certain form of lymphoma	2.1
Human immunodeficiency virus (HIV)	Kaposi sarcoma and non-Hodgkin lymphoma	
Human papillomavirus (HPV)	Anal, cervical, head and neck, oral, penile, vaginal, and vulvar cancers	30
Human T-cell lymphotrophic virus, type-1 (HTLV-1)	T-cell leukemia and lymphoma	0.1
Merkel cell polyomavirus (MCV)	Merkel cell carcinoma	

* where known

Data from (95)

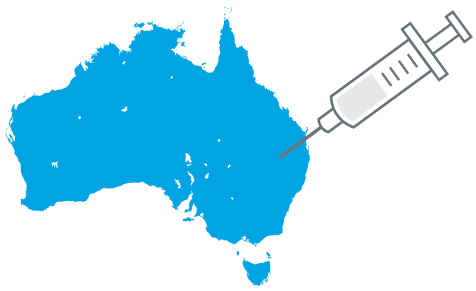
PREVENTING OR ELIMINATING INFECTION WITH THE FOUR MAIN CANCER-CAUSING PATHOGENS

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
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
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	CDC and USPSTF recommend screening those born from 1945 to 1965 for HCV infection
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 • women up to age 26 and men up to age 21 who did not receive the vaccine or complete the course as preteens. See sidebar on **HPV vaccination recommendations**, p. 37

CDC, Centers for Disease Control and Prevention; HPV, hepatitis B virus; HCV, hepatitis C virus; HPV, human papillomavirus; MALT, mucosa-associated lymphoid tissue; USPSTF, U.S. Preventive Services Task Force. Adapted from (36).

arsenic exposure is a well-established cause of bladder and skin cancer, which is why, in 2006, the EPA lowered the maximum contaminant level for arsenic in public water systems from 50 to 10 micrograms per liter. As a result, the urinary arsenic content in individuals who used public water was significantly reduced between 2003 and 2014 (104). These reductions in exposure translated to an estimated 900 fewer cases of lung and bladder cancers or 50 fewer cases of skin cancer per year (104).

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 (14, 16). 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.



In Australia, high uptake of HPV vaccination has led to **a reduction from 23% (2007) to 1.5% (2015)** in the prevalence of vaccine-targeted HPV types, among women ages 18-24 (99).

HPV VACCINATION RECOMMENDATIONS

13 **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 in 2014 for
  - preventing anal, cervical, vaginal, and vulvar cancers and precancers, as well as genital warts.
  - vaccination of females ages 9 to 26 and males ages 9 to 15.

The U.S. Centers for Disease Control and Prevention (CDC) and the Advisory Committee on Immunization Practices (ACIP) announced updated guidelines for HPV vaccination in October, 2016. According to the updated recommendations (100):

- Two doses of HPV vaccine, given at least 6 months apart, are now recommended for adolescents younger than age 15 (except immunocompromised persons), rather than three doses.
- Three doses of HPV vaccine are still recommended for teenagers and young adults ages 15 to 26 and for people with weakened immune systems.

The updated recommendations are based on clinical data showing that, in younger adolescents, two doses of the vaccine trigger an immune response equivalent to that produced by three doses among adolescent girls and young women (101).

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 four types of cancer for which screening tests have been used widely to screen large segments of the U.S. population who are generally healthy and at average risk for the cancer being screened for.
- Every person has a unique risk for each type of cancer based on his or her genetic, molecular, and cellular makeup, and his or her lifetime exposures to cancer risk factors.
- Some people are at increased risk for certain types of cancer and may need to take risk-reducing measures, including adhering to a personalized cancer screening program.
- There are significant disparities in cancer screening rates among certain segments of the U.S. population.
- We need to develop new strategies to ensure optimal implementation of cancer screening for all.

Research has shown that most cancers arise and progress because of the accumulation of genetic mutations that disrupt the orderly processes controlling the multiplication and life span of normal cells (see **Understanding Cancer Development**, p. 17). There are numerous factors that cause cells to acquire genetic mutations, including exposure to toxicants in tobacco smoke and UV light.

Knowledge of the causes, timing, sequence, and frequency of the genetic, molecular, and cellular changes that drive cancer initiation and development provides opportunities to develop screening tests that can find, if present, precancerous lesions or cancer at an early stage of development (see **Figure 7**, p. 39). If precancerous lesions are detected, they can be removed before they become cancer, something that is referred to as cancer interception. Finding cancer early, before it has spread to other parts of the body, makes it more likely that a cancer can be intercepted, and a patient treated successfully.

WHAT IS CANCER SCREENING AND HOW IS IT DONE?

Cancer screening means checking for precancerous lesions or cancer in people who have no signs or symptoms of the cancer for which they are being checked but who are at risk for the disease (see **Consensus on Using Cancer Screening Tests**). People who have signs or symptoms suggesting the possible presence of cancer should see their health care providers promptly (see sidebar on **Signs and Symptoms of Cancer**, see p. 40).

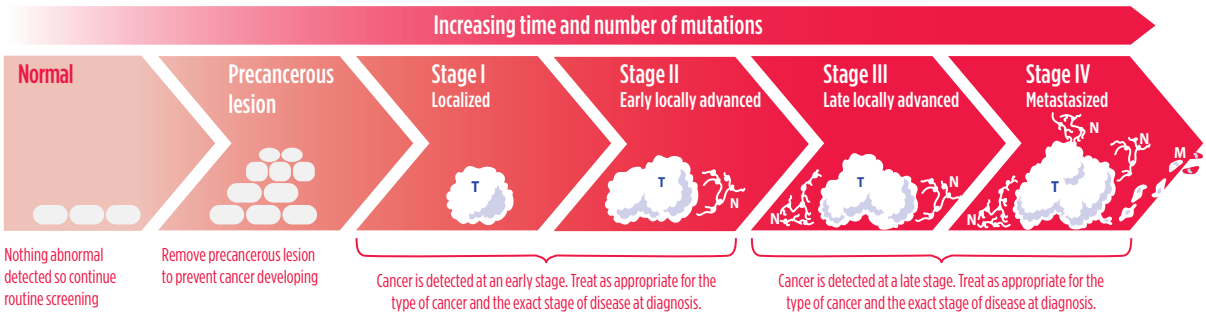
There are four types of cancer for which screening tests have been developed and used to screen large segments of the U.S. population who are generally healthy and at average risk for the cancer being screened for (see sidebar on **Cancers for Which Screening of Average-risk Individuals Has Been or Is Recommended**, p. 41).

CONSENSUS ON USING CANCER SCREENING TESTS

Screening for cancer has many benefits, but it also has potential risks (see sidebar on **Cancer Screening**, p. 42). This is why cancer screening is not recommended for everyone. Determining whether and for whom a cancer screening test can decrease deaths from the screened cancer and provide benefits that outweigh the potential risks requires extensive research and careful analysis of the data generated.

FIGURE 7

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 point, there is nothing that can be detected with cancer screening tests but the cell is predisposed to becoming cancerous. As the cell multiplies and acquires more mutations, it gains precancerous characteristics, and an increasingly abnormal precancerous lesion becomes detectable. Over time, as additional mutations accumulate, the precancerous lesion evolves into a cancerous lesion (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 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. It 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. It 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. 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. Removing a precancerous lesion or treating early-stage cancer is called cancer interception.

Adapted from (36).

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 rigorously evaluates data regarding the benefits and potential risks of cancer screening tests to make evidence-based recommendations about the use of these tests. These volunteer experts form the U.S. Preventive Services Task Force (USPSTF). The evidence-based USPSTF recommendations fall into several categories, most prominently 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 re-evaluates existing recommendations as new research becomes available and can revise the recommendations if necessary. For example, the USPSTF revised its recommendations for prostate cancer screening in 2018 (105). The revision was from recommending against screening to recommending that men ages 55–69 talk to a health care provider about the benefits and potential harms of screening before deciding if it is right for them.

Many professional societies also convene panels of experts to evaluate data regarding the benefits and potential risks of cancer screening tests, and each society 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 benefits and potential risks than other groups do, this can result in differences in recommendations from distinct groups of experts. For example, in 2018, the American Cancer Society began recommending that average-risk individuals start screening for colorectal cancer at age 45, rather than waiting until age 50 as the USPSTF and other professional societies recommend (106).

The existence of different cancer screening recommendations can make it challenging for individuals at average risk of those cancers to ascertain for which cancers to be screened and when. Nevertheless, there is more consensus than disagreement among recommendations about the use of the screening tests for the four types of cancer for which screening of generally healthy, average-risk individuals in large segments of the U.S. population has been or is recommended (see sidebar on **Consensus among Cancer Screening Recommendations for Average-risk Individuals**,

SIGNS AND SYMPTOMS OF CANCER

Cancer can cause many different signs and symptoms, including:

- **skin changes**, such as new moles or a change in an existing mole.
- **a sore** that does not heal.
- **breast changes**, such as
  - change in size or shape of the breast or nipple;
  - change in texture of breast skin;
  - new lump
- **a thickening or lump** on or under the skin.
- **hoarseness** or **persistent cough**.
- **problems with eating,** such as discomfort after eating, hard time swallowing, or changes in appetite.
- **changes in bowel habits.**
- **difficult or painful urination.**
- **weight gain or loss** with no known reason.
- **abdominal pain.**
- unexplained **night sweats.**
- **unusual bleeding or discharge,** including blood in the urine or stool, or vaginal bleeding.
- **feeling weak or very tired.**

People who have signs or symptoms suggesting the possible presence of cancer should see their health care providers promptly. However, it is important to remember that most often these symptoms are not likely due to cancer. For more information see https://www.cancer.gov/about-cancer/diagnosis-staging/symptoms.

In a recent study, **only 5.6 percent of adults** correctly answered the following four true or false questions about cancer screening, highlighting a lack of accurate knowledge about the topic and the need for improved education:

(i)
These tests can definitely tell that a person has cancer (false);

(ii)
When a test finds something abnormal, more tests are needed to know if it is cancer (true);

(iii)
When a test finds something abnormal, it is very likely cancer (false);

(iv)
The harms of these tests and exams sometimes outweigh the benefits (true) (107).

p. 44). The differences among the recommendations of different groups of experts highlight the areas in which more research is needed to determine more clearly the relative benefits and potential risks of screening, to develop new screening tests that have clearer benefits and/or lower potential risks, or to better identify people for whom the benefits of screening outweigh the potential risks.

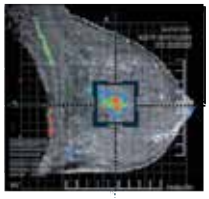
For individuals at average risk of developing a cancer for which there is a screening test, age and gender are the two main characteristics used to identify those for whom screening is recommended (see sidebar on **Consensus Among Cancer Screening Recommendations for Average-risk Individuals**, p. 44). However, each average-risk person is unique in his or her genetic, molecular, cellular, and tissue makeup (see sidebar on **Breast Density**, p. 43), lifetime exposures to cancer risk factors, general health, and tolerance of the potential risks of a screening test. Therefore, every individual should consult with his or her health care practitioner to develop a cancer prevention and early detection plan tailored to his or her situation.

A person's situation can change over the course of his or her lifetime; for example, a woman whose screening mammogram leads to a breast biopsy that reveals certain noncancerous breast conditions, such lobular carcinoma in situ, is now at increased risk for breast cancer. Therefore, it is important that individuals keep up a dialog with their

CANCERS FOR WHICH SCREENING OF AVERAGE-RISK INDIVIDUALS HAS BEEN OR IS RECOMMENDED

Highlighted here are cancer screening tests that have been used, at some time or another, to screen large segments of the U.S. population who are at average risk for the cancer being screened for. When to use these tests and in whom is discussed elsewhere (see Consensus Among Cancer Screening Recommendations for Average-risk Individuals, p. 44).

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).

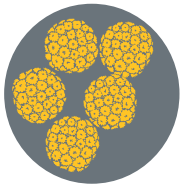
In most cases, the image is 2-dimensional, but some machines generate 3-dimensional images in a process called breast tomosynthesis.

Can detect breast cancers that cannot be felt. These cancers can be 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.

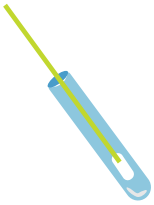
Can detect precancerous or cancerous cervical lesions, but the aim of screening is to find them at the earliest possible stage.



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 follow-up is recommended.

Colorectal Cancer



Stool tests: Some test for the presence of blood in stool samples. Others test for both blood and certain molecular alterations linked to colorectal cancer.

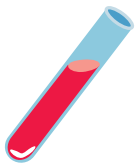
Do not directly detect colorectal precancerous lesions or cancers, but identify people for whom further testing is recommended.

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, but the aim of screening is to find them at the earliest possible stage so that they can be removed.

Computed tomography (CT) colonography (virtual colonoscopy) and double-contrast barium enema: Use X-rays to image the colon and rectum.

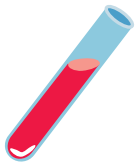
Can detect colorectal precancerous lesions or cancers, but the aim of screening is to find them at the earliest possible stage so that they can be removed.



Blood test: Detects epigenetic abnormalities linked to colorectal cancer in blood.

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

Prostate Cancer



PSA test: Measures the level of the protein 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.

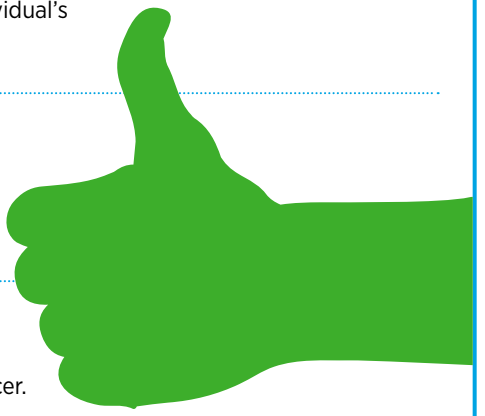
Adapted from (36)

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 7**, p. 39).

Reduced incidence of advanced disease. Screening tests that detect cancers at an early stage of development can reduce an 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 7**, p. 39).



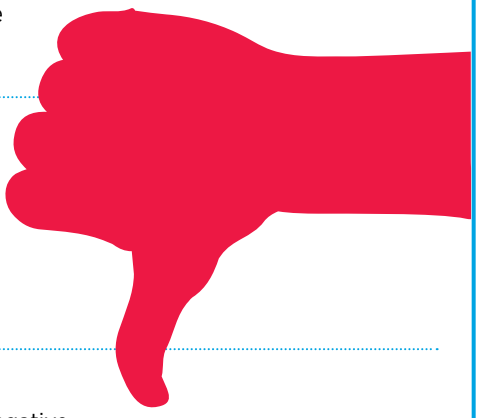
Reduced cancer mortality. Diagnosis at an early stage of disease can increase the likelihood that a patient can be successfully treated, which thereby reduces the individual's risk of dying from the screened cancer.

Reduced cancer treatment needs. Diagnosis at an early stage often can increase the likelihood that a patient can be successfully treated with less treatment.

Potential Risks 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 high 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; follow-up tests (such as biopsy procedures) are necessary to confirm or disprove a cancer diagnosis. 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 intervention.

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 may carry its own risks and costs. The rates of overdiagnosis and overtreatment vary among screening tests and will require more longitudinal studies to elucidate and quantify these rates.

Adapted from (1)

health care practitioners and continually evaluate their cancer screening plans, updating them if necessary.

Some individuals are at increased risk of certain cancers because they inherited a cancer-predisposing genetic mutation (see **Table 3**, p. 20). If a person has a family or personal history of cancer and thinks that he or she is at high risk for inheriting such a mutation, he or she should consult his or her health care practitioner and consider genetic testing (see sidebar on **How Do I Know If I Am at High Risk for Developing an Inherited Cancer?**). Given that researchers are constantly learning more about the genetic causes of cancer, the number of mutations linked to cancer risk increases over time (25). Thus, it is important that individuals at high risk for inheriting a cancer-predisposing genetic mutation keep up a dialog with their health care practitioners and continually evaluate whether genetic testing is available and/or right for them. There are 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 direct-to-consumer tests. As a result 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.

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

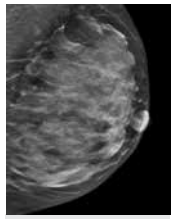
According to the National Cancer Institute, some of the factors to consider are whether, in your family, there is one or more of the following (108):

- several close blood relatives with the same type of cancer, such as a mother, daughter, and sisters with breast cancer;
- members diagnosed with cancers at younger ages than usual, such as colon cancer in a 20-year-old;
- one or more members who have more than one type of cancer, such as a female relative with both breast and ovarian cancer;
- one or more members with cancers in both of a pair of organs, such as both eyes, both kidneys, or both breasts;
- members with a type of cancer usually occurring in the opposite sex, such as a male relative with breast cancer.

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.
- 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 40's have dense breasts.
- Women who have dense breasts have a higher risk of developing breast cancer compared with women with less dense breast tissue. However, having 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 an individual woman's risk for the disease.
- Because dense breast tissue and breast cancer 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 are 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.

Images courtesy of Dr. Sabala Mandava, Henry Ford Health System

CONSENSUS AMONG CANCER SCREENING RECOMMENDATIONS FOR AVERAGE-RISK INDIVIDUALS

The U.S. Preventive Services Task Force (USPSTF) and many professional societies have evidence-based recommendations about the use of cancer screening tests among individuals who are at average risk for developing the cancers being screened for. Here, we highlight consensus, as of July 31, 2018, among these recommendations from the 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), and the American Urological Association (AUA). Not all of the professional societies have recommendations for every cancer screening test.

Breast Cancer Screening

There is consensus among the ACOG, ACS, NCCN, and USPSTF that women ages 50–74 who are at **average risk** for breast cancer should have regular screening mammograms. However, there is variability about whether the screening mammogram should be done every year or every other year.

Some of these groups recommend starting regular screening mammograms before age 50. It is important to note, however, that the groups recommending delay of screening mammography until age 50 do support women ages 40–49 having the opportunity to undergo regular screening mammograms if they decide that it is right for them.

Cervical Cancer Screening

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

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

Colorectal Cancer Screening

There is consensus among the ACS, ACP, NCCN, and USPSTF that adults ages 50–75 who are at **average risk** for colorectal cancer should be screened.

Some professional societies recommend starting regular screening before age 50 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 a health care provider to decide when to start screening and to choose the test that is right for them.

Prostate Cancer Screening

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

Some of the professional societies have additional recommendations that cover people who fall outside the age groups highlighted here and people who are at increased risk for certain cancers. To find out more about cancer screening recommendations see: http://www.uspreventiveservicestaskforce.org/, http://www.cancer.org/, http://m.acog.org/, https://www.auanet.org/, https://www.acponline.org/, and https://www.nccn.org/.

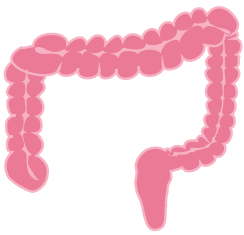
Adapted from (36).

If a person is at increased risk for developing a certain type or types of cancer, he or she should consult with his or her health care practitioner to tailor risk-reducing measures to his or her personal needs. Some people 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 (see sidebar on **Examples of Cancer Screening for Increased-risk Individuals**). Yet others may consider taking a preventive medicine or having risk-reducing surgery (see **Table 5**, p. 46 and **Supplemental Table 1**, p. 135).

As we increase our understanding of the genetic, molecular, and cellular characteristics of precancerous lesions, the

EXAMPLES OF CANCER SCREENING FOR INCREASED-RISK INDIVIDUALS

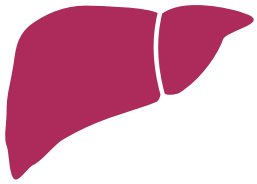
The U.S. Preventive Services Task Force (USPSTF) and many professional societies have evidence-based recommendations about the use of cancer screening tests among individuals who are at increased risk for developing the cancers being screened for. Here, we highlight some examples of recommendations for cancer screening increased-risk individuals, as of July 31, 2018, from the USPSTF, the United States Multi-Society Task Force (MSTF) on colorectal cancer, the National Comprehensive Cancer Network (NCCN), and the American Cancer Society (ACS).



Colorectal Cancer

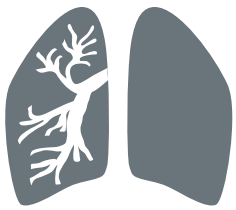
Several groups of individuals are at **increased risk** for colorectal cancer. Colorectal cancer screening recommendations vary for these different groups but all involve increased use of the screening tests used to screen average-risk individuals. For example:

- the NCCN and MSTF on colorectal cancer recommend that individuals at **high risk** because they inherited a genetic mutation that causes Lynch syndrome (see **Table 3**, p. 20) 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;
- the NCCN and MSTF on colorectal cancer recommend that individuals at **increased risk** because they have a first-degree relative who has been diagnosed with colorectal cancer or with an advanced adenoma(s) (an advanced precancerous lesion) should start screening with colonoscopy at age 40 or 10 years before the youngest case was diagnosed, whichever is earlier; and,
- the MSTF on colorectal cancer recommends that because African-Americans are at **increased risk** for colorectal cancer they should begin screening at age 45.



Liver Cancer

The NCCN recommends that individuals at **increased risk** for liver cancer because they have been diagnosed with either cirrhosis of the liver or as a carrier of the hepatitis B virus be screened every 6 months by ultrasound with or without a blood test for α-fetoprotein.



Lung Cancer

There is consensus among the ACS, NCCN, and USPSTF that screening with low-dose computed tomography should be limited to adults ages 55–74 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.

The USPSTF recommends annual screening for these individuals, whereas the ACS and NCCN recommend these individuals talk to a physician about the benefits and potential harms of screening before deciding if it is right for them.

inherited genetic mutations that increase a person's risk for certain types of cancer, and the biology of cancer, we will be able to identify new biomarkers and develop new screening tests for more types of cancer (25, 109, 110). We will also be able to better tailor cancer prevention and early detection to the individual patient, ushering in a new era of precision cancer prevention (111, 112).

SUBOPTIMAL USE OF CANCER SCREENING TESTS

Not all average-risk individuals are up to date with cancer screening recommendations (see sidebar on **Consensus among Cancer Screening Recommendations for Average-risk Individuals**, p. 44). For example, a substantial percentage of individuals for whom the U.S. Preventive Services Task Force recommended screening were not up to date with screening in 2015, which is the last year for which these data are currently available (114):

28.5%	of women ages 50–74 were not up to date with breast cancer screening.
17%	of women ages 21–65 were not up to date with cervical cancer screening.
38%	of adults ages 50–75 were not up to date with colorectal cancer screening.

CANCER SCREENING TESTS ARE BEING USED SUBOPTIMALLY

Even though the benefits of screening defined groups of individuals at average risk for breast, cervical, and colorectal cancer outweigh the potential risks (see sidebar on **Consensus among Cancer Screening Recommendations for Average-risk Individuals**, p. 44), many individuals for whom screening is recommended do not get screened (see sidebar on **Suboptimal Use of Cancer Screening Tests**). In addition, a recent study found that just 2 percent of adults for whom lung cancer screening is recommended because they are at high risk for developing the disease had undergone screening in 2016 (113). Individuals who are not up to date with screening recommendations are disproportionately found in certain groups (see sidebar on **Disparities in Cancer Screening**, p. 47) (114).

The suboptimal use of cancer screening tests and the significant disparities in cancer screening rates among certain segments of the U.S. population highlight the need for new strategies and public policies to increase cancer screening access and uptake. Identifying strategies to achieve this goal is an area of intensive research investigation. For example, one recent study showed that actively reaching out to adults not up to date with colorectal cancer screening by mailing them information about colorectal cancer risk and either sending them a stool test or following up by phone to schedule a colonoscopy increased screening uptake (116). Another study found that colorectal cancer screening rates were increased when patients attending a primary care appointment were provided access to an in-office app educating them about colorectal screening and allowing them to order their preferred test (117). Yet another study showed that a religiously tailored, mosque-based education program increased receipt of mammograms among Muslim American women (118).

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	Stomach cancer	Gastrectomy	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

Education is a vital part of all efforts to ensure optimal implementation of cancer screening. Clearly there is a lot more to do in this regard because a recent study found that just 20 percent of adults knew that the potential risks of cancer screening tests sometimes outweigh the benefits (107). Increasing awareness of this fact among adults above the recommended age cutoff for a given cancer screening test and those with life-limiting medical conditions is particularly important because a substantial proportion of adults in these categories continue screening even though the evidence indicates that the benefits of screening are unlikely to outweigh the potential harms for them (119-121). One study found that the way in which health care practitioners put forward information can heavily influence whether older adults continue screening (119).

DISPARITIES IN CANCER SCREENING

There are disparities in adherence to United States Preventive Services Task Force cancer screening recommendations among certain segments of the U.S. population. These disparities include (114, 115):

SIGNIFICANTLY MORE LIKELY

64% VERSUS 48%	Whites are significantly more likely to be up to date with colorectal cancer screening than **American Indians/Alaska Natives**, 64% versus 48%.
79% VERSUS 59%	Women in the highest income bracket are significantly more likely to be up to date with cervical cancer screening than **women in the lowest income bracket**, 79% versus 59%.
77% VERSUS 35%	Women who have private health insurance are significantly more likely to be up to date with breast cancer screening than **women who are uninsured**, 77% versus 35%.
76% VERSUS 58%	Adults in Massachusetts are significantly more likely to be up to date with colorectal cancer screening than those in **Wyoming**, 76% versus 58%.
83% VERSUS 75%	Straight women are significantly more likely to be up to date with cervical cancer screening than **gay women**, 83% versus 75%.
72% VERSUS 54%	U.S.-born women are significantly more likely than **foreign-born women who have lived in the United States for less than 10 years** to be up to date with breast cancer screening, 72% versus 54%.

HARNESSING RESEARCH DISCOVERIES FOR PATIENT BENEFIT

IN THIS SECTION, YOU WILL LEARN:

- Progress against cancer is driven by research discoveries.
- From August 1, 2017, to July 31, 2018, the FDA approved 14 new therapeutics for treating certain types of cancer.
- During the same period, the uses of 11 previously approved anticancer therapeutics were expanded by the FDA to include additional types of cancer.
- Our increasing understanding of the genetic, molecular, and cellular characteristics of cancer continues to spur the development of new molecularly targeted therapeutics.
- A groundbreaking new type of immunotherapy called CAR T-cell therapy was recently approved for treating certain types of cancer.
- Identifying ways to help survivors meet the many challenges they face after a cancer diagnosis is an important area of research investigation.

The dedicated efforts of individuals working throughout the cycle of biomedical research are benefiting people around the world by driving progress across the continuum of clinical cancer care (see **Figure 8**, p. 49).

BIOMEDICAL RESEARCH

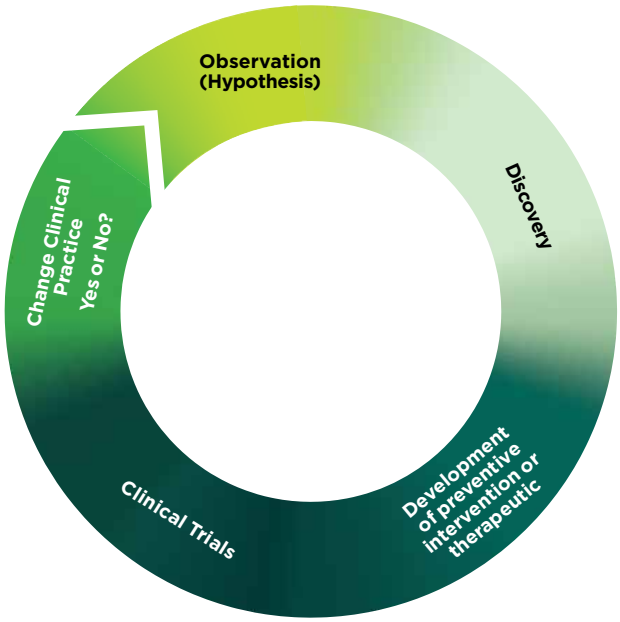
Biomedical research is an iterative cycle, with each discovery building on knowledge gained from prior research (see **Figure 8**, p. 49). In recent years, the cycle has become increasingly efficient as the pace of discovery has increased and new disciplines have been integrated. As a result of these changes, the pace at which research discoveries are being converted to lifesaving advances across the continuum of clinical cancer care has been accelerating (see **Figure 9**, p. 50). To maintain this momentum, it is imperative that we better support investigators throughout their careers, and especially those early in their careers.

The biomedical research cycle is set in motion when discoveries with the potential to affect the practice of medicine and public health are made in any area of biomedical research or clinical practice (see sidebar on **Biomedical Research: What Is It and Who Conducts It?** p. 52). The discoveries lead to questions, or hypotheses, that are tested by researchers performing experiments in a wide range of models that mimic what happens in healthy and diseased conditions. The results from these experiments can lead to the identification of a potential target for a preventive intervention or therapeutic, or the identification of a predictive or prognostic biomarker. They also can feed backward in the cycle by providing new discoveries that lead to more hypotheses.

After a potential target for a preventive intervention or therapeutic is identified, it takes many more years of research before a candidate preventive intervention or therapeutic is developed and ready for testing in clinical trials (see sidebar on **Developing Preventive Interventions and Therapeutics**, p. 53). During this time, candidates are rigorously tested to identify any potential toxicity and to determine the appropriate dose and dosing schedule for testing in a clinical trial.

Before most potential new diagnostic, preventive, or therapeutic products can be approved by the FDA and used as part of patient care, the safety and efficacy of the product must be rigorously tested through clinical trials. All clinical trials are reviewed and approved by institutional review boards before they can begin and are

FIGURE 8 THE BIOMEDICAL RESEARCH CYCLE



Results from any type of research can fuel the biomedical 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 preventive intervention or therapeutic (see sidebar on **Developing Preventive Interventions and Therapeutics**, p. 53). Before entering clinical testing, potential preventive interventions or therapeutics undergo preclinical testing to identify any toxicities and help determine initial dosing. Clinical testing is a multiphase process aimed at demonstrating the safety and efficacy of a potential preventive intervention or therapeutic. If an agent is safe and effective and 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 preventive intervention or therapeutic can feed back into the biomedical research cycle and further enhance the use of that agent or the development of others like it. If, however, a preventive intervention or therapeutic is not safe or effective and fails to gain FDA approval, the observations from the clinical testing still feed back into the biomedical 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 continuously powers new observations.

Adapted from (31).

monitored throughout their duration. There are several types of cancer clinical trials, including treatment trials, prevention trials, screening trials, and supportive or palliative care trials, each designed to answer different research questions.

Cancer clinical trials have traditionally been done in three successive phases (see **Figure 10**, p. 54). However, the traditional clinical testing process has required a large number of patients and taken many years to complete, making it extremely costly and one of the major barriers to rapid translation of scientific knowledge into clinical advances.

Over the past three 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 the assessment of therapeutics for life-threatening diseases such as cancer (123,124). In recent years, an increasing number of therapeutics have been approved by the FDA using one or more of these review strategies, including 12 of the 14 new anticancer therapeutics approved by the FDA during the 12 months spanning this report (125).

In addition, advances in our understanding of cancer biology have enabled researchers, regulators, and the pharmaceutical industry to develop new ways of designing, conducting, and reviewing clinical trials. Among the new ways to design clinical trials that have emerged in recent years are adaptive, seamless, and master protocol designs (126-128). These designs aim to streamline the 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 or not the anticancer therapeutic being evaluated is safe and effective, 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 effective.

Master protocol design clinical trials aim to answer multiple questions within a single overall clinical trial (128). The emergence of this clinical trial design has largely been driven by our increased understanding of the genetic mutations that lead to cancer initiation and growth.

Two examples of master protocol clinical trials are "basket" and "umbrella" trials (see **Figure 11**, p. 55). Basket trials test one given therapeutic on a group of patients who all have the same type of genetic mutation, regardless of the anatomic site of the original cancer. One basket trial that has led to an FDA approval for patients with a rare type of cancer characterized by a defined genetic mutation is highlighted in **Molecularly Targeting Blood Cancers** (see p. 63) (129). Umbrella trials test multiple therapeutics across multiple genetic mutations on a group of patients, all of whom have cancer arising in the same anatomic site.

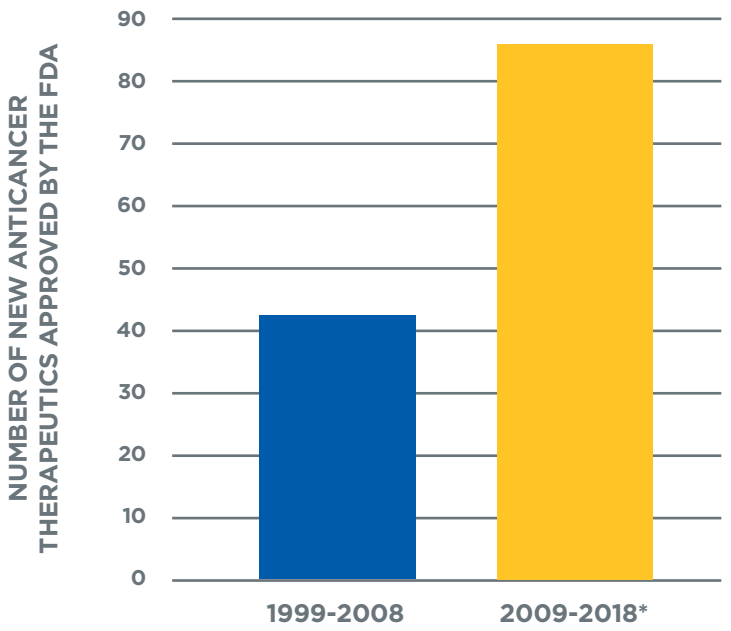
Fewer than 5 percent
of adults diagnosed with cancer participate in a cancer clinical trial (130).

Even though our growing knowledge of cancer biology has led to new ways of designing, conducting, and reviewing clinical trials that are yielding numerous 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 and a lack of diversity among those who do participate (see sidebar on **Disparities in Cancer Clinical Trial Participation**, p. 51) (130-133).

These challenges exist even though a poll of the general public showed that more than 30 percent of U.S. adults would be very willing to participate in a cancer clinical trial if asked (135). Thus, understanding the barriers to clinical trial participation for all segments of the population is vital if we are to ensure that all segments of the population benefit from advances against cancer. Current research shows that the barriers to participation are complex and interrelated but often include factors that reduce access to clinical trials such as lack of health insurance, low socioeconomic status, and lack of health literacy (130, 132). Overcoming these barriers will require all stakeholders in the biomedical research community to work together to develop a multifaceted approach that includes the development and implementation of new, more effective education and policy initiatives (see sidebar on **The Biomedical Research Community: Driving Progress Together**, p. 8).

FIGURE 9

DOUBLE THE PROGRESS



The pace at which research discoveries are being converted to new anticancer therapeutics has been accelerating in recent years, as illustrated by the fact that the number of new anticancer therapeutics approved by the U.S. Food and Drug Administration (FDA) from 2009 to 2018 was more than double the number approved by the agency in the decade before (1999–2008); 86 versus 42.

Data obtained from (122) and https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugInnovation/default.htm

**As of July 31, 2018*

PROGRESS ACROSS THE CLINICAL CANCER CARE CONTINUUM

The hard work of individuals throughout the biomedical research cycle constantly powers the translation of research discoveries 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 biomedical research cycle because observations made during the routine use of new medical products can be used to further enhance the use of those products, to accelerate the pace at which similar products are developed, or 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, 2017, to July 31, 2018. In particular, it focuses on the 14 new anticancer therapeutics approved by the FDA during this period (see **Table 1**, p. 9). Also highlighted are the 11 previously approved anticancer therapeutics that were approved by the FDA for treating additional types of cancer. 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 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.

New FDA-approved medical products are used alongside treatments already in use, including surgery, radiotherapy, and cytotoxic chemotherapy, which continue to be the mainstays of clinical cancer care (see **Figure 12**, p. 56) (see **Supplemental Table 2**, p. 136, and **Supplemental Table 3**, p. 139).

New medical products improve lives by having an effect across the continuum of clinical cancer care. However, not all patients receive the standard of care recommended for the type and stage of cancer that they have been diagnosed with (see sidebar on **Disparities in Cancer Treatment**, p. 57). Thus, it is imperative that all stakeholders in the biomedical research community, including advocates like **Karen Eubanks Jackson** (see p. 58), work together to address the challenge of disparities in cancer treatment because these can be associated with adverse differences in survival (136-139).

Treatment with Surgery, Radiotherapy, and Cytotoxic Chemotherapy

In the past two decades, we have witnessed the emergence of two new pillars of cancer care—molecularly targeted therapy

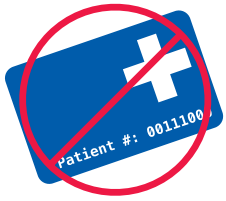
DISPARITIES IN CANCER CLINICAL TRIAL PARTICIPATION

If we are to ensure that investigational anticancer therapeutics are safe and effective for everyone who will use them if they are approved, it is vital that the participants in the clinical trials testing the agents represent the entire population who may use them. Despite this knowledge, several segments of the population have been found to be underrepresented in clinical trials. Examples of these disparities include the following:

The elderly (adults age 65 or older) accounted for about two-thirds of patients with breast, lung, colorectal, and prostate cancer, but only one-third of participants in clinical trials testing treatments for these four types of cancer (131).

Black and Hispanic patients with breast, lung, colorectal, and prostate cancer were almost 30 percent less likely to enroll in clinical trials testing treatments for these four types of cancer compared with white patients (131).

Patients with an annual household income of <$50,000 were 32 percent less likely to participate in a clinical trial compared with those who had an annual household income of ≥$50,000 (133).



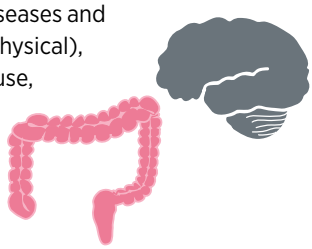
Individuals who lack insurance account for only 5 percent of those participating in clinical trials compared with 16 percent of the U.S. population (134).

and immunotherapy (see **Figure 12**, p. 56). The therapeutics that form these pillars of cancer care tend to be more effective and less toxic than the treatments encompassed by two of the long-standing pillars of cancer treatment—radiotherapy and cytotoxic chemotherapy. However, not all patients with cancer are treated with molecularly targeted therapy and/or immunotherapy. For some patients, this might be because there is no appropriate molecularly targeted therapeutic or immunotherapeutic available. For others, it may be that surgery, radiotherapy, and/or cytotoxic chemotherapy are the best treatment options (see sidebar on **Using Radiation in Cancer Care**, p. 60). Whatever the reason, the reality is that these traditional therapeutic modalities form the foundation of treatment for almost all patients with cancer.

BIOMEDICAL RESEARCH: WHAT IS IT AND WHO CONDUCTS IT?

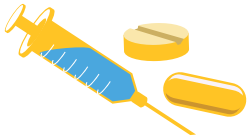
Biomedical research, as defined by the Organization for Economic Cooperation and Development, comprises:

The study of specific diseases and conditions (mental or physical), including detection, cause, prevention, treatment, and rehabilitation of persons.



The scientific investigation required to understand the underlying life processes that affect disease and human well-being, including areas such as the cellular and molecular bases of diseases, genetics, and immunology.

The design of methods, drugs, and devices used to diagnose, support, and maintain the individual during and after treatment for specific diseases or conditions.



Biomedical researchers are often categorized by the type of work they do, although some conduct several types of work and can be included in several categories. The types of biomedical researchers include, but are not limited to, the following:

Basic researchers study organisms, cells, molecules, or genes to gain new knowledge about cellular and molecular changes that occur naturally or during the development of a disease.

Clinical researchers conduct clinical trials; study a particular patient or group of patients, including their behaviors; or use materials from humans, such as blood or tissue samples, to do research on health and disease and to develop new treatments.

Population scientists, such as epidemiologists, social and behavioral scientists, and health services researchers, study the patterns, causes, costs, and effects of health and disease conditions in defined populations, or the effects of interventions on these conditions. These areas of research are highly collaborative and can span the spectrum from basic to clinical to population-wide research.

Physician-scientists care for patients and conduct research. They may perform population, clinical, or basic research.

Adapted from (1)

DEVELOPING PREVENTIVE INTERVENTIONS AND THERAPEUTICS

Target validation.
Potential therapeutic targets identified in discovery research are confirmed to play a causative role in a given disease.

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

Hit to lead.
Positive hits are further tested to determine which bind the target with the most specificity.

Lead optimization.
The properties of the lead compound are refined to enhance potency and drug availability and to reduce side effects.

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

IND

Investigational new drug.
Prior to clinical testing, one or more clinical candidates are submitted to the FDA for approval to be used in clinical trials.

Adapted from (1)

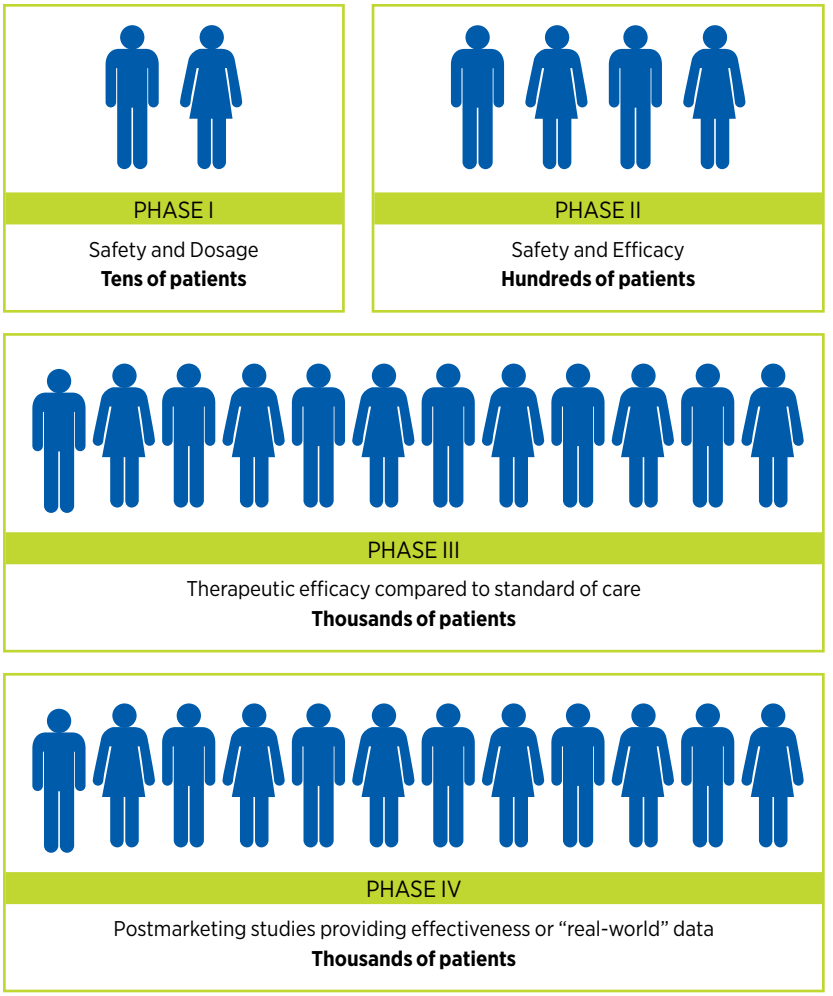
Importantly, the use of surgery, radiotherapy, and cytotoxic chemotherapy is constantly evolving as we develop new forms of these treatments and identify new ways to use those that we already have to improve survival and quality of life for patients. For example, two recent randomized phase II clinical trials suggest that local ablative radiotherapy can extend disease-free survival for patients with lung cancer who have limited metastases and whose disease has not progressed after initial systemic therapy (142,143). The following discussion focuses on some recent changes in the use of the three traditional pillars of clinical cancer care.

Refining the Use of Surgery, Radiotherapy, and Cytotoxic Chemotherapy

Even though surgery, radiotherapy, and cytotoxic chemotherapy are mainstays of cancer treatment, they can have long-term adverse effects on patients. This has led many researchers to investigate whether less aggressive treatment can allow some patients the chance of an improved quality of life without an adverse effect on survival. In the past few years, many approaches to treatment de-escalation have been implemented in the clinic through changes in treatment guidelines.

FIGURE **10**

THE TRADITIONAL APPROACH TO CANCER CLINICAL TRIALS

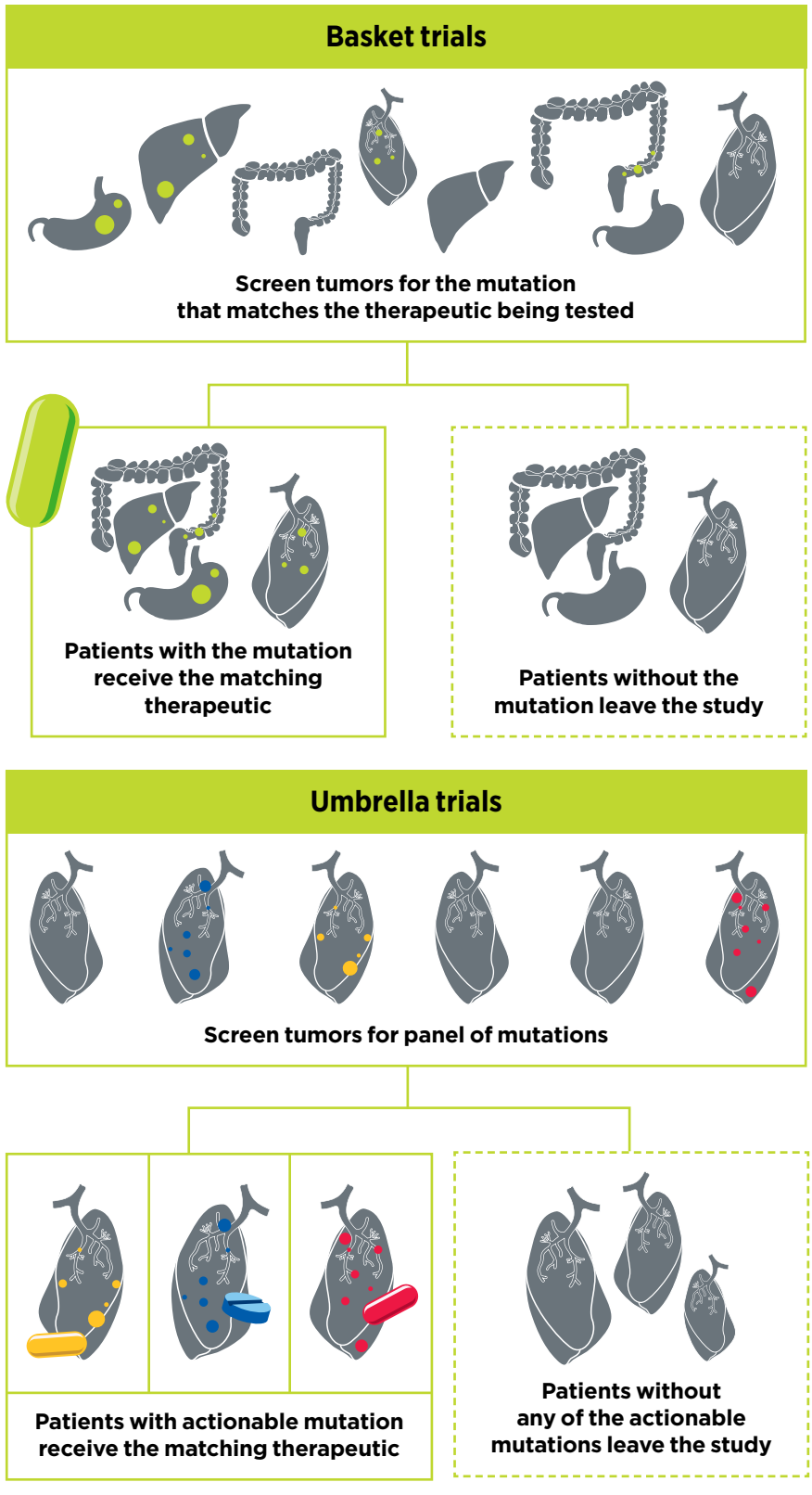


Cancer clinical trials evaluating potential new preventive interventions and therapeutics have traditionally been done in three successive phases, each with an increasing number of patients. Phase I studies are designed to determine the optimal dose of an investigational agent, how humans process it, and potential toxicities. Phase II studies are designed to determine the initial efficacy of an agent, in addition to continually monitoring for potential toxicities. Phase III studies are large trials designed to determine efficacy as compared to standard of care (placebos are rarely used in cancer treatment clinical trials). When successful, the results of these trials can be used by regulators to approve new preventive interventions or therapeutics, or new indications for existing agents. Phase IV studies are conducted after an agent is provisionally approved by the FDA and provide additional effectiveness or "real-world" data on the agent.

Adapted from (18).

FIGURE 11

MASTERING CLINICAL TRIAL DESIGN



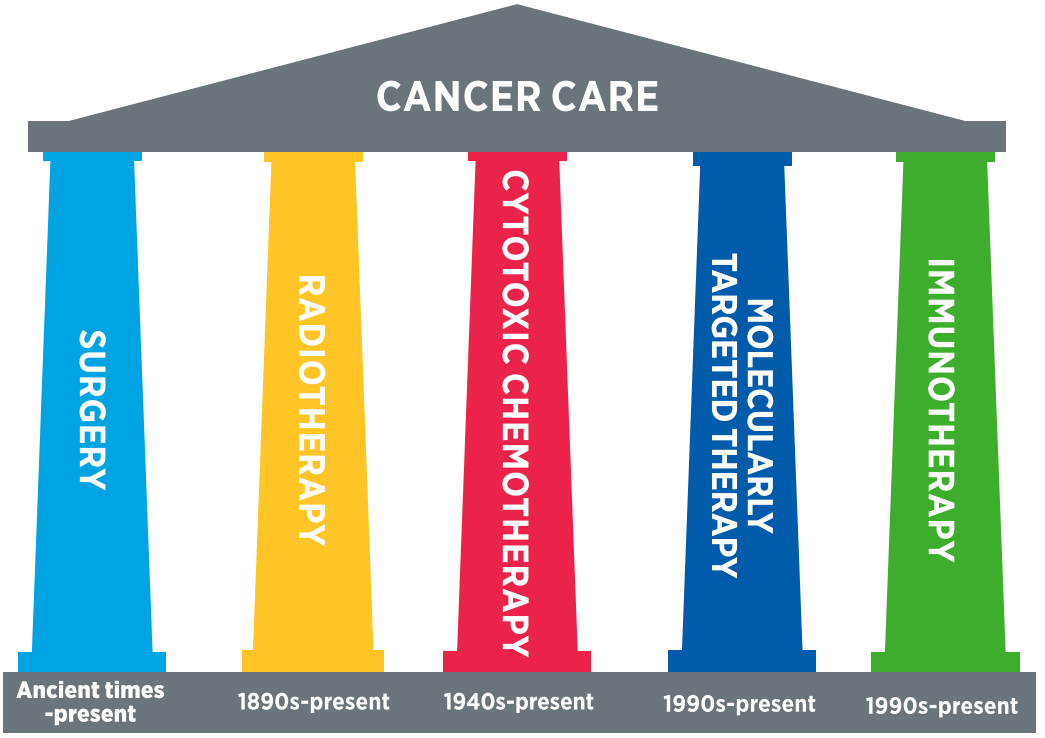
Recent advances in our understanding of cancer biology have led to new ways of designing and conducting clinical trials. One of the new approaches is to use a master protocol to answer multiple questions within a single overall clinical trial. Two types of master protocol clinical trial are basket and umbrella trials. These trials allow the development of new anticancer therapeutics to be streamlined. The right therapeutics are matched with the right patients earlier, which 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. 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. In the umbrella trial illustrated here, three different drugs are being tested against multiple genetic mutations (yellow, blue, and red dots) within lung cancer.

About 50 percent of U.S. cancer patients receive **radiotherapy** to shrink or eliminate tumors or to prevent local recurrence (141).

One example of this trend in cancer care for each of surgery, radiotherapy, and cytotoxic chemotherapy is highlighted in the sidebar **Less Is Sometimes More in Surgery, Radiotherapy, and Cytotoxic Chemotherapy** (see p. 61).

Identifying other situations in which treatment can be de-escalated is an area of intensive research investigation. Several clinical trials studying this have reported results recently and although the results have not yet led to a change in treatment guidelines, the approaches studied are being gradually adopted into clinical practice. For example, stereotactic radiosurgery, which can more precisely target radiation to tumors than traditional radiotherapy, is increasingly being used after surgical removal of a brain metastasis (a tumor that has spread from another part of the body to the brain) because it was shown to cause less

FIGURE 12 **THE PILLARS OF CANCER CARE**



Physicians often refer to the "pillars" of cancer treatment. For many years, there was just 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, radiation, and cytotoxic chemotherapy—continue to be the mainstays of cancer care. However, in the late 1990s, the first molecularly targeted therapeutics were introduced, leading to the fourth pillar, molecularly targeted therapy, which continues to grow. 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 (31).

neurocognitive deficit compared with whole brain radiation (151). Stereotactic radiosurgery in this medical situation has also been shown to reduce local relapse compared to observation alone (152). In addition, recent results from a large national clinical trial showed that genetic profiling of particular types of breast cancer has the potential to identify women who can safely avoid chemotherapy (153).

Targeting Radiotherapy to Neuroendocrine Tumors

The FDA recently provided oncologists with a new way to use radiotherapy in the treatment of patients with certain types of neuroendocrine tumors when it approved two targeted radiotherapeutics, lutetium (Lu) 177 dotatate (Lutathera) and iobenguane iodine (I) 131 (Azedra) (see sidebar on **Using Radiation in Cancer Care**, p. 60). Lu-177 dotatate was approved for treating gastroenteropancreatic neuroendocrine tumors in January 2018 and iobenguane I-131 was approved for treating pheochromocytomas and paragangliomas in July 2018.

Neuroendocrine tumors arise in cells called neuroendocrine cells, which are specialized hormone-producing cells found in most organs of the body. Gastroenteropancreatic neuroendocrine tumors are among the most common of these cancers. They arise in the pancreas and different parts of the gastrointestinal tract, such as the stomach, intestines, colon, and rectum. Pheochromocytomas and paragangliomas are rare neuroendocrine tumors that arise in the adrenal glands, and along nerve pathways in the head and neck, and in other parts of the body, respectively.

Research has shown that most neuroendocrine tumors have the protein somatostatin receptor on the surface. When the hormone somatostatin attaches to somatostatin receptor on the surface of a cell, it has a suppressive effect on the functions of the cell. This body of knowledge has led to the development of several medical products used in the care of patients with neuroendocrine tumors, including Lu-177 dotatate (see **Figure 13**, p. 62).

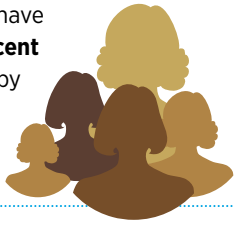
In Lu-177 dotatate, the radionuclide Lu-177 is linked to a molecule that is analogous to somatostatin. Molecules like this are called somatostatin analogs. The somatostatin analog component of Lu-177 dotatate targets the radiation-emitting component Lu-177 to the somatostatin receptor-positive cancer cells.

Lu-177 dotatate was approved for treating adults with somatostatin receptor-positive gastroenteropancreatic neuroendocrine tumors after it was shown in a phase III clinical trial to increase the time to disease progression by more than six-fold (155). This approval is very good news for patients, like **Nicole DiCamillo** (see p. 64),

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 standard recommended cancer treatments. Examples of these disparities include:

African-American women who have stage I breast cancer are **18 percent less likely** to receive radiotherapy after a lumpectomy compared with white women (140).

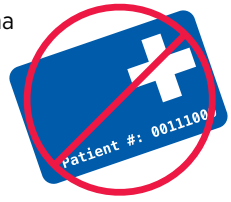


Patients with metastatic bladder cancer who are of low socioeconomic status are **50 percent less likely** to receive chemotherapy compared with those of high socioeconomic status (136).

Patients with small-cell lung cancer without detectable metastases who lack health insurance are **25 percent less likely** to receive radiotherapy compared with those who have private or managed care insurance (137).

Black patients who have multiple myeloma are **21 percent less likely** to receive the molecularly targeted therapeutic bortezomib (Velcade) compared with white patients (138).

Patients with stage III melanoma who lack insurance are **31 percent less likely** to receive immunotherapy compared with those who have private insurance (139).



" ... we need to do more because **breast cancer continues to be a serious life-threatening health issue for African-American women.** "

INCREASING AWARENESS OF BREAST CANCER IN THE AFRICAN-AMERICAN COMMUNITY

Twenty-five years ago, my life changed when my doctor told me, "You have breast cancer." I researched to look for a national African-American organization that provided education and support for breast cancer survivors in my community. I wanted to feel a sisterhood, unity, and have support. When I discovered there was no such organization I founded Sisters Network Inc. Our primary goal has always been to increase local and national awareness of the devastating impact that breast cancer has in the African-American community. We have made an impact in elevating breast health awareness in the black community over the last 24 years, but we need to do more because breast cancer continues to be a serious life-threatening health issue for African-American women.

In 1993, I was living a great life in Los Angeles. I was recently married, had a great career, and exercised regularly. The idea that I might have cancer was not on my radar, especially not breast cancer. I had had annual mammograms since my late 30's and not one of them revealed breast cancer.

I started having annual mammograms earlier than most women because my aunt died in her early 40's from breast cancer. I wanted to be proactive about monitoring my health. Over the years I had three biopsies after mammograms showed something suspicious but each biopsy came back negative for cancer.

When I started having a strange feeling in my right breast, I was concerned and decided I needed to go to my doctor. It wasn't pain, but the sensation was with me all the time. I knew my body and knew something was wrong. I asked my doctor what tests were available to find an explanation. Because my annual mammogram had shown no sign of cancer, he sent me for an ultrasound.

I am thankful that I asked my doctor to address my health concerns because the ultrasound showed a 3.5-centimeter tumor in my right breast. I was ultimately diagnosed with stage II breast cancer. If I hadn't been proactive about my health and paid attention to my body, the cancer would not have been caught early and I don't think I would be here today.

After consulting with my doctors, I chose breast-conserving surgery, which was relatively new at the time. The surgery was followed by six weeks of radiation and six months of chemotherapy. These treatments were hard but I got through it all. I'm living proof that you can survive breast cancer and its treatments and find a new normal.

Ever since my diagnosis, my husband Kyle and daughter Caleen have given me incredible support. They have been there for me in every way possible. I am grateful for their support, but from the very beginning, I felt something was missing. I needed to connect with other women like me; women from my community who were going through the same experience.

When I could not find what I was looking for, I stepped out on faith without any funding, just a borrowed desk and my home telephone, and formed the national sisterhood that I craved. My vision was to establish a national organization that would provide African-American women with resources and knowledge to navigate after being diagnosed with breast cancer. The organization also would educate the community by raising awareness of the devastating impact of breast cancer on African-American women. At the time, fear of all forms of cancer was rampant in the African-American community. No one wanted to talk about the "C word" and people felt that less information was better than more. I was passionate about changing this way of thinking, because I knew that knowledge is power.

Sisters Network has come a long way since then and has developed affiliate chapters across the country with dedicated survivors and community. By raising awareness about the disease—how it can be prevented, detected, and treated—and providing financial support to help women with their financial challenges we are making a difference in the community across the country.

However, the breast cancer death rate remains unacceptably high among African-American women, and much more needs to be done to educate the community, provide access to cutting-edge care, and increase participation in clinical trials. We all need to work together to achieve these goals if we are to save more lives today and in the future.

USING RADIATION IN CANCER CARE

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

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

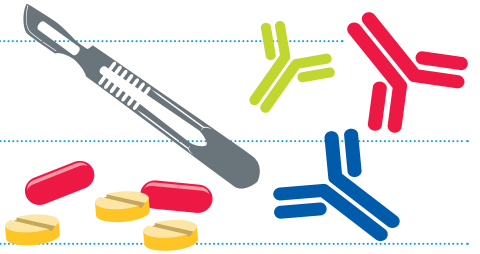
Radiotherapy

- Radiotherapy is the use of high-energy rays (e.g., gamma rays and X-rays) or particles (e.g., electrons, protons, and carbon nuclei) to control or eliminate cancer.

- Radiotherapy works chiefly by damaging DNA, leading to cell death.

Uses of Radiotherapy

Curative radiotherapy seeks to eliminate cancers, particularly small cancers, as well as locally advanced cancers as part of combination therapy.



Neoadjuvant radiotherapy is used to reduce or control a cancer so that it can be subsequently treated by a different method such as surgery.

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

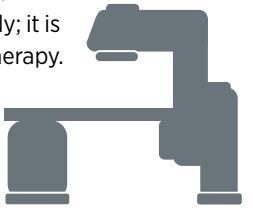
Palliative radiotherapy is used to reduce or control symptoms of disease when cure by another method is not possible.

Types of Radiotherapy

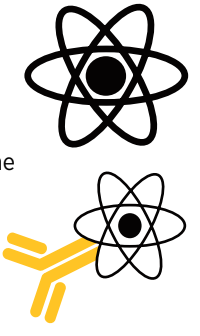
Particle therapy uses protons or carbon ions rather than X-rays as the source of energy. In contrast to X-rays that pass though the body, losing energy and causing damage to the noncancerous tissues through which they pass, these heavier particles deposit most of their energy in the target. In this manner, 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 the patient is still being determined.

Brachytherapy places small radioactive sources in or next to the tumor either temporarily or permanently.

External beam radiotherapy encompasses several types of radiotherapy that direct radiation at the tumor from outside the body; it is the most common form of radiotherapy. Electrons and photons (X-rays) are the most common sources of radiation in external beam radiotherapy.



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 (see **Targeting Radiotherapy to Neuroendocrine Tumors**, p. 57).



Adapted from (31)

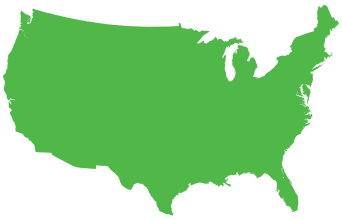
because there are very few treatment options for what can be a debilitating disease.

Research has shown that most pheochromocytomas and paragangliomas have a protein called the norepinephrine transporter on the surface. It functions to take up norepinephrine, a chemical messenger that transmits signals from one nerve cell to another. This knowledge led to the development of iobenguane I-131.

Iobenguane, which is also known as metaiodobenzylguanidine (MIBG) is a molecule that is analogous to norepinephrine. In iobenguane I-131, the iobenguane is labeled with the radionuclide I-131. Imaging using iobenguane labeled with either I-131 or I-123 has been used to locate pheochromocytomas and paragangliomas in the body during diagnosis and treatment monitoring since the early 1980s.

Azedra is a new version of iobenguane I-131 that delivers more radiation to tumors than the version used for imaging. It was approved for treating patients age 12 and older with locally advanced or metastatic pheochromocytoma or paraganglioma whose tumors test positive for the norepinephrine transporter during

Neuroendocrine tumors are rare.



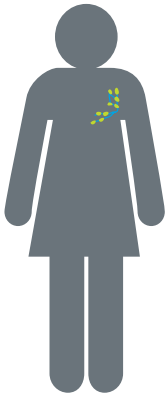
Each year in the United States:

only about
one in every 27,000 adults
is diagnosed with
gastroenteropancreatic
neuroendocrine tumors;

approximately
100–200 individuals
are diagnosed with
pheochromocytomas
and paragangliomas.

LESS IS SOMETIMES MORE IN SURGERY RADIOTHERAPY, AND CYTOTOXIC CHEMOTHERAPY

Researchers have learned that less aggressive surgery, radiotherapy, and cytotoxic chemotherapy can be appropriate for some patients, allowing them an improved quality of life without an adverse effect on their survival. Here we highlight one example of treatment de-escalation for each of these therapeutic modalities:



In 2016, the American Society of Clinical Oncology introduced new guidelines recommending that an invasive surgical procedure called axillary lymph node dissection was no longer needed for a defined group of women with breast cancer (144). New research showing that these women had equally good disease-free and overall survival after 10 years whether or not they had an axillary lymph node dissection provides additional support for the guideline change (145).

In 2018, the American Society for Radiation Oncology introduced new guidelines recommending expanding the use of hypofractionated radiotherapy for treating breast cancer (146). This change was spurred by research showing that hypofractionated radiotherapy, whereby patients receive fewer but higher doses of radiotherapy over a shorter time period compared with the traditional course of radiotherapy, is as effective as the traditional course of radiotherapy and has fewer adverse effects (147–150).

In 2018, the National Comprehensive Cancer Network recommended reducing the length of time certain patients with colon cancer received cytotoxic chemotherapy after surgery has removed the cancer.

iobenguane imaging. The approval was based on results from a phase II clinical trial that showed that 22 percent of patients treated with iobenguane I-131 had tumor shrinkage (156).

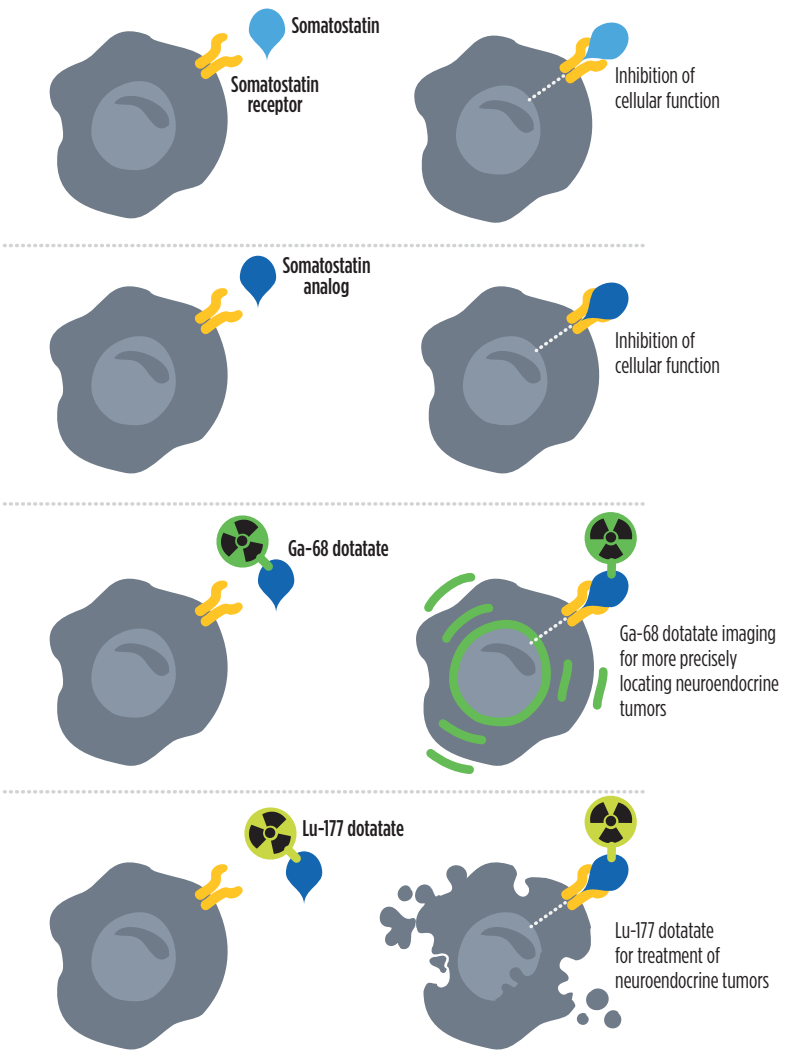
Improving Outcomes with Nanotechnology

Acute myeloid leukemia (AML) is projected to be the second most common type of leukemia diagnosed in the United States in 2018 and the leading cause of leukemia-related death (10). Treatment changed little from the 1970s until 2017, when four new therapeutics were approved by the FDA (157). One of these new therapeutics was discussed in the *AACR Cancer Progress Report 2017* (18), two are discussed below (see **Molecularly Targeting Blood Cancers**, p. 63), and the fourth is a nanodrug called Vyxeos.

Nanotechnology refers to the manufacturing of objects with dimensions one million times smaller than a millimeter (the smallest width of a human hair is just 50 times smaller than a millimeter). Nanomedicine is the application of nanotechnology to the research and practice of medicine. Nanodrugs comprise an anticancer therapeutic (or therapeutics) and a nanosized carrier

FIGURE 13

HARNESSING KNOWLEDGE IN MULTIPLE WAYS



Since the discovery of somatostatin in 1973, researchers have learned much about the hormone, its natural biological functions, and the ways in which it exerts these functions (154). They have learned that the main function of somatostatin is to inhibit the function of cells. It does this by attaching to proteins called somatostatin receptors on the surface of cells, sending signals that suppress the functions of the cells. Research has also shown that most neuroendocrine tumors have somatostatin receptors on the surface. This body of knowledge was first harnessed to develop agents that mimic the effects of somatostatin, so-called somatostatin analogs. These agents have been used to treat patients with neuroendocrine tumors since the late 1980s. This provided the foundation for the development of radiolabeled somatostatin analogs. A somatostatin analog linked to the radionuclide gallium (Ga) 68 was approved by the U.S. Food and Drug Administration (FDA) in June 2016 for use with positron emission tomography–computed tomography (PET–CT) to help physicians more precisely locate neuroendocrine tumors in the body during diagnosis (36). Then, in January 2018, the FDA approved a second radiolabeled somatostatin analog, lutetium (Lu) 177 dotatate (Lutathera), for treating patients with gastroenteropancreatic neuroendocrine tumors.

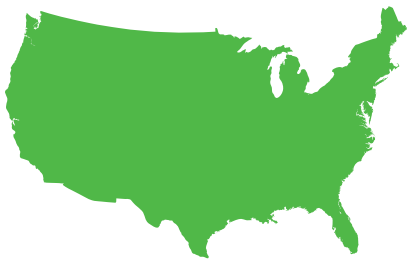
that selectively delivers the anticancer therapeutic to the cancer and protects the anticancer therapeutic from being destroyed by the body. As a result, nanodrugs allow the delivery of higher levels of anticancer therapeutic to cancer cells than traditional systemic delivery methods, increasing effectiveness while reducing toxic side effects.

In the case of Vyxeos, the nanosized carriers are liposomes, and the anticancer therapeutics are two of the cytotoxic chemotherapeutics most commonly used to treat AML, daunorubicin and cytarabine. Daunorubicin and cytarabine are currently given separately. With Vyxeos, patients receive a fixed combination of these two cytotoxic chemotherapeutics formulated together in a single nanodrug.

The FDA approved Vyxeos in August 2017 for treating adults with two types of AML that have particularly poor outlooks: newly diagnosed therapy-related AML and AML with myelodysplasia-related changes. The approval was based on results from a phase III clinical trial that showed that patients who received Vyxeos had significantly improved overall survival compared with those who received separate treatments of daunorubicin and cytarabine (158).

Guiding Surgery Magnetically

For many patients with breast cancer, a mastectomy is an early step in their treatment. During surgery, in addition to removing the breast tissue, the surgeon often removes the lymph node or nodes to which the cancer is most likely to first spread from the initial tumor. These lymph nodes are called sentinel lymph nodes. The presence or absence of cancer cells in these nodes helps determine the extent of the disease and provides information that is central to the development of the rest of the patient's treatment plan.



19,520 new AML cases in the United States in 2018; **10,670 deaths** (10).

To identify the sentinel lymph nodes, patients are injected with a radioactive substance, a blue dye, or both. The surgeon then uses a device that detects radioactivity to find the sentinel node(s) and/or looks for lymph nodes that are stained with the blue dye. In July 2018, the FDA approved a new system for guiding surgeons to sentinel lymph nodes in patients with breast cancer who are undergoing a mastectomy. When using the Magtrace and Sentimag Magnetic Localization System, patients are injected with a magnetic tracer and the surgeon uses a magnetic probe to find the sentinel node(s). The new system was approved after it was shown in a clinical trial to be as good as using both a radioactive substance and blue dye at detecting sentinel lymph nodes. It provides a new option for surgeons and patients who may want to avoid using radioactive materials.

Treatment with Molecularly Targeted Therapeutics

The discovery of the genetic underpinnings of cancer set the stage for the new era of precision medicine, an era in which the standard of care for many patients is changing from a one-size-fits-all approach to one in which greater understanding of the patient and his or her tumor dictates the best treatment option for the patient (see **Understanding Cancer Development**, p. 17).

Therapeutics directed to the molecules involved in different aspects of the cancer process 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, 2017, to July 31, 2018, the FDA approved nine new molecularly targeted anticancer therapeutics (see **Table 1**, p. 9). During this period, they also approved six previously approved molecularly targeted anticancer therapeutics for treating additional types of cancer.

Molecularly Targeting Blood Cancers

Cancers that arise in blood-forming tissue, such as the bone marrow, or in the cells of the immune system are called blood cancers, or hematologic cancers. Seven recent FDA decisions have added molecularly targeted therapeutics as a treatment option for patients with a wide array of hematologic cancers (see sidebar on **Recent Advances against Blood Cancers**, p. 66).

" It **[Lutathera] is the best thing that has happened** for me and for my family. "

LIVING FAMILY LIFE TO THE FULL
THANKS TO LUTATHERA

I was diagnosed with cancer almost 14 years ago. Over the years, I have had many treatments that have controlled the cancer. But until my most recent treatment, Lutathera, none stopped the stomach and intestinal issues that greatly reduced my quality of life. Lutathera is amazing. Not only is it shrinking the tumors, it is allowing me to live a normal life with my husband and kids. Before Lutathera, I could barely make it from my bed to the bathroom without help. Now, I am doing better than I ever have.

When I was diagnosed with cancer in 2004, the type of cancer I have was called carcinoid cancer. Now it is called gastroenteropancreatic neuroendocrine tumor.

Even though I received the diagnosis at 27, I had been having what I now know were symptoms of the cancer since I was a teenager. I suffered flashes; I was always throwing up; I constantly needed the bathroom. My mom took me to see lots of doctors. None of them could pinpoint the problem. Some of them even told me there was nothing wrong with me.

Somehow, I lived with the endless stomach and intestinal issues but it severely limited what I could do.

The events leading to my diagnosis began when I was 7 months pregnant. After an uncomplicated pregnancy, I went into labor prematurely, and my son was born at 32 weeks. Three weeks after the delivery, I was back in the hospital because of severe pain in my abdomen, which I put down to an infection at the site of the caesarian section incision. But I ended up having surgery to remove my gallbladder and some gallstones. During the surgery, the doctor took a biopsy of a cyst that he noticed, the results of which revealed carcinoid cancer.

All this happened in early December 2004 but I didn't find out about the cancer diagnosis until after Christmas. The doctors had told my parents but I was in no state to learn the news. I had a premature baby to care for and major abdominal surgery to recover from.

When my parents sat me down and told me I had cancer, I was angry. I was angry because after all those years of being told that nothing was wrong, it turns out I had cancer all that time. I was angry because I had just been blessed with a newborn son and now I feared that I might die. I was angry because I could see how much the diagnosis hurt my parents; they had been by my side through everything and hadn't been able to get the answers we needed.

Then, I looked at my son and I knew that I had to overcome the cancer; I had to make it.

My first treatment was an exploratory surgery. They opened me up and removed a few tumors in my stomach and a large tumor in my intestines, which is what had sent me into premature labor; it was literally pushing my son out. There were also more than 175 tumors in my liver, which they could not remove.

After the surgery, the doctor told me to get my affairs in order. He said that I wouldn't live past 30. I could not fathom it. I was being told that I wouldn't see my son lose his first tooth, go to kindergarten, and grow up and graduate.

It turns out he was wrong. Since my diagnosis, I have had many surgeries, chemoembolizations, bland embolizations, and radiofrequency ablations to remove tumors. I have also received octreotide (Sandostatin). While all the treatments have helped, I remained significantly restricted by the ongoing stomach and intestinal side effects of the cancer. I could rarely get through a whole day at work. I couldn't go to my kids' school and sports events.

Then, in 2016, I started seeing a new doctor and received four treatments of Lutathera through a compassionate use program.

Since those treatments, each CT scan that I have had has shown my tumors are shrinking. My doctor recently changed my follow-up CT schedule from every three months to every four months and says he might move it to every six months soon.

Lutathera has changed my life. I never take days off work. I coach my son's soccer team. I watch my kids' concerts. I spent a whole day enjoying the rides with my family at Universal Studios. I couldn't even have dreamed of doing these things before Lutathera. It is the best thing that has happened for me and for my family.

RECENT ADVANCES AGAINST BLOOD CANCERS

In the 12 months spanning August 1, 2017 to July 31, 2018, the FDA approved new treatment options for certain patients with the following seven types of blood cancer, or hematologic cancer:

Acute Lymphoblastic Leukemia (ALL) in adults

- Inotuzumab ozogamicin (Besponsa) is a molecularly targeted therapeutic approved in August 2017.

ALL in Children and Young Adults

- Tisagenlecleucel (Kymriah) is an immunotherapeutic and gene therapy approved in August 2017.

Acute Myeloid Leukemia (AML)

- Enasidenib (Idhifa) is a molecularly targeted therapeutic approved in August 2017.
- Vyxeos is a fixed combination of the cytotoxic chemotherapeutics daunorubicin and cytarabine formulated together in a single nanoformulation approved in August 2017.
- Gemtuzumab ozogamicin (Mylotarg) is a molecularly targeted therapeutic approved in September 2017.
- Ivosidenib (Tibsovo) is a molecularly targeted therapeutic approved in July 2018.

Cutaneous T-cell lymphoma

- Brentuximab vedotin (Adcetris) is a molecularly targeted therapeutic approved in November 2017.

Erdheim-Chester Disease

- Vemurafenib (Zelboraf) is a molecularly targeted therapeutic approved in November 2017.

Follicular Lymphoma

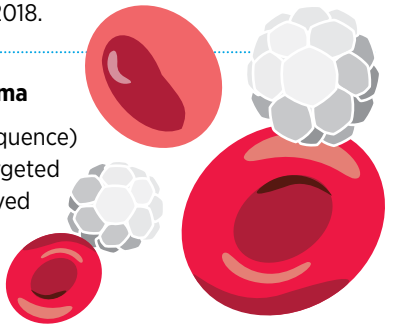
- Copanlisib (Aliqopa) is a molecularly targeted therapeutic approved in September 2017.

Large B Cell Lymphoma

- Axicabtagene ciloleucel (Yescarta) is an immunotherapeutic and gene therapy approved in October 2017.
- Tisagenlecleucel is an immunotherapeutic and gene therapy approved in May 2018.
- Pembrolizumab (Keytruda) is an immunotherapeutic approved in June 2018.

Mantle Cell Lymphoma

- Acalabrutinib (Calquence) is a molecularly targeted therapeutic approved in October 2017.



As discussed earlier in the report (see **Improving Outcomes with Nanotechnology**, p. 62), AML is projected to be the second most common type of leukemia diagnosed in the United States in 2018 (10). In recent years, research has substantially increased our understanding of the biology of AML, in particular the genetic mutations that promote leukemia development (159). This is fueling the emergence of molecularly targeted therapeutics for defined groups of patients with the disease.

Two of the genes known to be mutated in a significant proportion of AML cases are IDH1 and IDH2 (159). This led researchers to develop enasidenib (Idhifa), a therapeutic that targets the altered IDH2 proteins generated by IDH2 mutations, and ivosidenib (Tibsovo), a therapeutic that targets the altered IDH1 proteins generated by IDH1 mutations. Enasidenib and ivosidenb were approved by the FDA in August 2017 and July 2018, respectively, for treating adults who have AML that has not responded to or has relapsed after other treatment, and that harbors a mutation in either the IDH2 or IDH1 gene, respectively, as detected by an FDA-approved test, or companion diagnostic (see sidebar on **Companion Diagnostics**). At the same time that the molecularly targeted therapeutics were approved, the FDA approved companion diagnostics, the RealTime IDH2 Assay to identify patients with AML with an IDH2 mutation and the RealTime IDH1 Assay to identify patients with AML with an IDH1 mutation.

Enasidenib was approved for the treatment of AML after it was shown that 19 percent of patients treated with the molecularly targeted therapeutic in a phase I/II clinical trial had complete remission, meaning that there was no evidence of disease and full recovery of blood counts after treatment (160). The approval of this new molecularly targeted therapeutic is providing new hope for patients like **Chuck Dandridge** (see p. 68).

Ivosidenib was approved for the treatment of AML after it was shown that 25 percent of patients treated with the

27 percent of AML patients

live **five or more years** after diagnosis (3).

molecularly targeted therapeutic in a phase 1 clinical trial had complete remission (161).

In September 2017, the FDA approved another molecularly targeted therapeutic for the treatment of AML. Gemtuzumab ozogamicin (Mylotarg) is a type of molecularly targeted therapeutic known as an antibody-drug conjugate. These therapeutics use an antibody to deliver an attached cytotoxic chemotherapeutic directly to the cancer cells that have the antibody's target on their surfaces. Once the antibody attaches to its target on the surface of a cancer cell, the antibody-drug conjugate is internalized by the cells. This leads to the cytotoxic chemotherapeutic being released from the antibody. Once free, it is toxic to the cancer cells, which ultimately die. The precision of antibody targeting reduces the side effects of the cytotoxic chemotherapeutic compared with traditional systemic delivery.

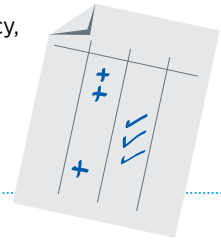
In the case of gemtuzumab ozogamicin, the cytotoxic chemotherapeutic calicheamicin is attached to a CD33-targeted antibody. In most patients, AML cells have the molecule CD33 on the surface. The recent approval of gemtuzumab ozogamicin is for these patients. This approval followed an approval in 2000 for patients more than 60 years of age who had AML that had relapsed or who were unable to be treated with standard chemotherapy. However, the FDA requested that gemtuzumab ozogamicin be withdrawn from that use in 2010 after results from a clinical trial showed that the antibody-drug conjugate might not benefit patients and raised safety concerns. These challenges have been overcome through two approaches; the new approval is for a lower recommended dose of gemtuzumab ozogamicin and for use of the molecularly targeted therapeutic in a more precisely defined patient population, those with CD33-positive AML.

Two other antibody-drug conjugates have been approved recently by the FDA for treating patients with particular types of hematologic cancer. Inotuzumab ozogamicin (Besponsa) was approved for treating certain adults with acute lymphoblastic leukemia (ALL) in August 2017. In

COMPANION DIAGNOSTICS

The effective use of anticancer therapeutics targeting particular 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;

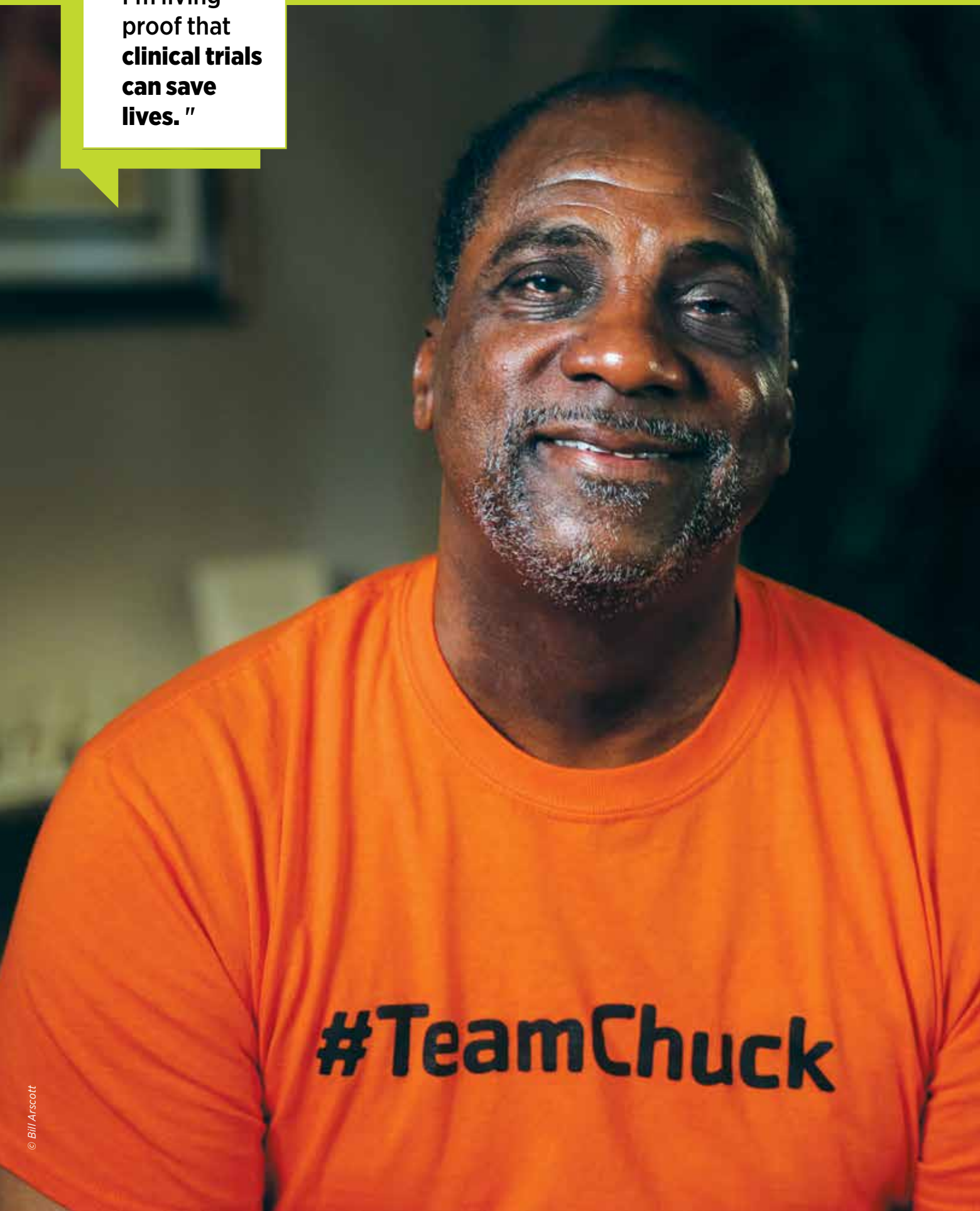
accurately match patients with the most appropriate therapy;

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 any adverse side effects.

Adapted from (1)

" I'm living proof that **clinical trials can save lives.** "



SURVIVING ACUTE MYELOID LEUKEMIA THANKS TO CLINICAL TRIALS

Since being diagnosed with acute myeloid leukemia in September 2014, I have taken part in two clinical trials. The pioneering treatments I received through these clinical trials were successful and I feel back to normal, 100 percent.

It all started in March 2014. I was visiting my primary care physician for a routine blood test to monitor my health because I take a statin to control my cholesterol levels. The test showed that my blood cell counts were slightly lower than normal. After another two blood tests confirmed the result, my doctor suggested I see a local oncologist.

The oncologist diagnosed me with myelodysplastic syndrome, or MDS. I didn't have any symptoms. I was living my normal life. But the oncologist explained that MDS was a precursor to leukemia and that over time I would begin to feel unwell if I didn't start treatment. I took azacitidine for about eight to ten months to try keep the disease in check. But the number of abnormal cells, or blasts, in my bone marrow kept rising and my disease progressed to acute myeloid leukemia, or AML.

At this point, the oncologist told me that my only option for a cure would be a stem cell transplant. He suggested I consider being treated at one of the large cancer centers in Texas because they would be more oriented to these procedures.

The first place I visited was UT Southwestern in Dallas. The doctor I met made me feel really comfortable. She explained the disease and how there were lots of new treatments being developed for the type of leukemia I had. I felt my anxiety level come down, and decided there and then that this was the place where I would continue treatment.

Many of the options mentioned by my doctor were for people whose leukemia had abnormalities in certain genes, so my leukemia cells were tested to see if I was a match for any of the new treatments. They found a mutation in a gene called IDH2, which made me eligible for a clinical trial testing a medication called AG221 [enasidenib; Idhifa].

After listening to the doctor and discussing everything with my family, I decided to enroll in the clinical trial. I knew that even if AG221 did not help me, the results of the clinical trial would help the researchers and help other patients in the future.

I took four pills every morning for eight months. They did not get rid of the leukemia completely but they did lower the number of blasts in my bone marrow dramatically. Without that, I would not have been able to have the stem cell transplant that has eliminated the leukemia.

Then, because there were no donors who were a good match for me, I had to receive the stem cell transplant through a clinical trial that was testing a way to use cells from a partially matched donor using genetic engineering.

The way the doctor explained the trial to me is that the problem with using a partially matched donor is that the transplanted cells can cause something called graft-versus-host disease, which is when the transplanted cells attack parts of the body. This can be life-threatening. The genetic engineering was being done so that if I got severe graft-versus-host disease, the transplanted cells could be eliminated.

My son was my donor. They took his cells and sent them away to be genetically engineered. That process took about 3 1/2 weeks. During that time, I was admitted to the hospital for chemotherapy to wipe out all the leukemia and my own immune system. I was in isolation because I was at very high risk of getting an infection.

The doctors then infused genetically engineered stem cells and immune cells called T cells from my son. I was the first person in the United States to have this type of transplant.

Currently, I have a blood test every three months and see the doctor every six months. Fortunately, I never got severe graft-versus-host disease so the doctors did not have to eliminate my son's cells using the genetic modification they had engineered into the cells, and the latest tests showed that my blood counts are good and that the transplant worked.

I am truly blessed. I am doing great. I feel extremely healthy and am back in the gym working out. I'm living proof that clinical trials can save lives.

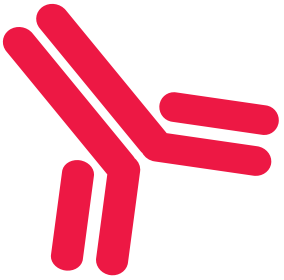
most cases, ALL arises in immune cells called B cells, which have a protein called CD22 on the surface. Inotuzumab ozogamicin comprises a CD22-targeted antibody linked to the same cytotoxic chemotherapeutic that is found in gemtuzumab ozogamicin, calicheamicin. The approval of the new molecularly targeted therapeutic for treating adults with B-cell precursor ALL that has not responded to or has relapsed after another treatment was based on results from a phase III clinical trial. These results showed that the rate of complete remission for those who received inotuzumab ozogamicin was more than double the rate for those who received standard chemotherapy (162).

In November 2017, brentuximab vedotin (Adcetris) was approved for treating primary cutaneous anaplastic large cell lymphoma and CD30-expressing mycosis fungoides, which are types of cutaneous T-cell lymphoma. Cutaneous T-cell lymphomas are types of non-Hodgkin lymphoma that arise in immune cells called T cells. In nearly all cases of primary cutaneous anaplastic large cell lymphoma and many cases of mycosis fungoides, the cancerous T cells have a molecule called CD30 on the surface. Brentuximab vedotin comprises the cytotoxic agent monomethyl auristatin E attached to a CD30-targeted antibody using a linker. It was approved for treating adults who have primary cutaneous anaplastic large cell lymphoma or CD30-expressing mycosis fungoides that has progressed despite prior treatment. The approval was based on results from a phase III clinical trial showing that more than 50 percent of patients who received brentuximab vedotin had either partial or complete tumor shrinkage compared with 13 percent of patients who received cytotoxic chemotherapy (163). In addition, the time that patients had no disease progression was more than four times longer among those who were treated with brentuximab vedotin. The new approval for brentuximab vedotin followed previous approvals for classical Hodgkin lymphoma and systemic anaplastic large cell lymphoma in 2012.

Acalabrutinib (Calquence) is a new molecularly targeted therapeutic that the FDA approved for treating a type of non-Hodgkin lymphoma called mantle cell lymphoma in October 2017. Like many other hematologic cancers, mantle cell lymphoma arises in B cells. Acalabrutinib targets a protein called Bruton tyrosine kinase (BTK), which is one component of a signaling pathway that promotes the survival and expansion of mantle cell lymphoma B cells. The approval of acalabrutinib for treating patients with mantle cell lymphoma that has not responded to or has relapsed after another treatment was based on results from a phase II clinical trial. These results showed that 40 percent of patients treated with the molecularly targeted therapeutic had complete tumor shrinkage and another 41 percent had partial tumor shrinkage (164).

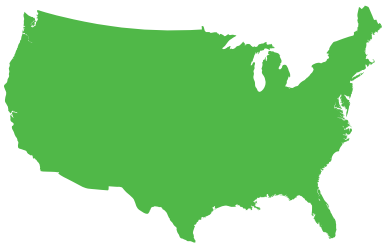
Copanlisib (Aliqopa) is another new molecularly targeted therapeutic approved recently by the FDA. It was approved for treating adults who have follicular lymphoma that has relapsed after they have received at least two other treatments. Follicular lymphoma is another type of non-Hodgkin lymphoma that arises in B cells. Copanlisib targets a molecule called phosphatidylinositol 3-kinase, which is a component of a signaling pathway that has a key role in promoting the survival and expansion of follicular lymphoma B cells. Copanlisib was approved after 14 percent of patients with follicular lymphoma who received the molecularly targeted therapeutic through a phase II clinical trial had complete tumor shrinkage (165). Another 44 percent of the trial participants had partial tumor shrinkage.

In November 2017, the FDA approved the molecularly targeted therapeutic vemurafenib (Zelboraf) for treating a rare hematologic cancer called Erdheim-Chester disease. Erdheim-Chester disease arises through overproduction of a type of immune cell called a histiocyte. Genomic analysis has shown that more than 50 percent of these cancers are fueled by specific mutations in the BRAF gene, called the BRAF V600 mutations. Vemurafenib targets BRAF proteins generated by BRAF V600 mutations.



There are **4 antibody-drug conjugates** approved by the FDA for treating different types of cancer: ado-trastuzumab emtansine (Kadcyla) for certain types of breast cancer, brentuximab vedotin (Adcetris) for certain types of lymphoma, gemtuzumab ozogamicin (Mylotarg) for certain types of leukemia, and inotuzumab ozogamicin (Besponsa) for certain types of leukemia.

Cutaneous T-cell lymphoma is a rare type of cancer;



fewer than 3,000 U.S. adults are diagnosed with it each year.

Erdheim-Chester disease

is estimated to affect just **600 to 700 patients worldwide.**

Vemurafenib was first approved by the FDA in August 2011 for treating patients with melanoma positive for a specific BRAF V600 mutation, the BRAF V600E mutation. Its success as a treatment for these patients led researchers to launch a phase II basket trial in which they evaluated vemurafenib as a treatment for patients with any type of cancer harboring any BRAF V600 mutation, except for patients with melanoma (129) (see **Figure 11**, p. 55). Vemurafenib treatment led to tumor shrinkage in more than half of the 22 patients with BRAF V600 mutation–positive Erdheim-Chester disease who were enrolled in the trial (166). As a result, the FDA approved vemurafenib for the treatment of patients like these.

Increasing Options for Patients with Breast Cancer

Despite major advances in the treatment of breast cancer, the disease is the second-leading cause of cancer-related death for women in the United States (10). Recent FDA decisions have the potential to power even more progress against breast cancer because they have provided new treatment options for certain patients with the disease.

For many patients with breast cancer, one factor determining which treatment options could be considered is the presence or absence of three tumor biomarkers, two hormone receptors (HRs) and HER2. About 70 percent of breast cancers diagnosed the United States are characterized as hormone receptor–positive, HER2-negative (13). Potential treatment options for these patients include therapeutics such as tamoxifen, which works by preventing the hormone estrogen from attaching to its receptor, and aromatase inhibitors, which work by lowering the level of estrogen in the body. Treatment with these therapeutics is often called endocrine therapy.

Unfortunately, most advanced, hormone receptor–positive breast cancers that initially respond to endocrine therapy eventually progress because they have become treatment resistant (see sidebar on **The Challenge of Treatment Resistance**, p. 73). Recently, the FDA approved the molecularly targeted therapeutic abemaciclib (Verzenio) for use in several ways to help address this challenge.

Abemaciclib works by blocking the function of two proteins that play a role in driving cell multiplication—cyclin-dependent kinase (CDK) 4 and CDK6. In September 2017, the FDA approved abemaciclib for treating adults with hormone receptor–positive, HER2-negative, advanced or metastatic breast cancer that has progressed during or after endocrine therapy and/or cytotoxic chemotherapy. This approval was based on results from two clinical trials (167, 168). One, a phase III clinical trial, showed that adding abemaciclib to fulvestrant (a type of endocrine therapy) increased the time before disease progressed for patients who had previously received endocrine therapy but not cytotoxic chemotherapy (167). The other, a phase II clinical trial, showed that abemaciclib alone led to complete or partial tumor shrinkage for some patients whose metastatic disease had been treated with endocrine therapy and cytotoxic chemotherapy (168).

In February 2018, the FDA added an approval for using abemaciclib in combination with an aromatase inhibitor as an initial treatment for postmenopausal women with hormone receptor–positive, HER2-negative, advanced or metastatic breast cancer. This approval was based on results from a phase III clinical trial that showed that adding abemaciclib to aromatase inhibitor treatment for this group of patients almost doubled the time to disease progression (169).

Another recent FDA decision that is a major advance in breast cancer treatment is the approval of the molecularly targeted therapeutic olaparib (Lynparza) for treating those patients with HER2-negative, metastatic breast cancer who have already received cytotoxic chemotherapy and who have inherited a known or suspected cancer-associated mutation in the BRCA1 or BRCA2 gene. At the same time, the FDA granted marketing authorization for a companion diagnostic, the BRACAnalysis CDx test, to help identify patients with breast cancer with a known or suspected cancer-associated mutation in the BRCA1 or BRCA2 gene (see sidebar on **Companion Diagnostics**, p. 67).

About 5 percent of all breast cancers diagnosed in the United States are attributable to an inherited mutation in the BRCA1 or BRCA2 gene (170).

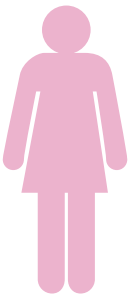
Olaparib targets poly ADP-ribose polymerase (PARP) proteins. Decades of basic research have shown that a key function of both PARP and BRCA proteins is repairing damaged DNA (see **Figure 14**, p. 74). Although they work in different DNA repair pathways, the pathways are interrelated and disruption to both pathways can ultimately trigger cell death. As a result, cancer cells harboring cancer-associated BRCA gene mutations that disable the ability of BRCA proteins to repair damaged DNA are particularly susceptible to PARP inhibitors, which work, at least in part, by blocking the DNA repair function of PARP proteins.

Olaparib was first approved by the FDA in December 2014 for treating women with advanced ovarian cancer who have inherited a known or suspected cancer-associated mutation in the BRCA1 or BRCA2 gene. Its success as a treatment for these patients led researchers to test whether the molecularly targeted therapeutic might also benefit patients with breast cancer who have inherited a known or suspected cancer-associated mutation in the BRCA1 or BRCA2 gene, like **Lisa Quinn** (see p. 76). Olaparib was approved for these patients after it was shown in a phase III clinical trial to significantly increase the time to disease progression compared with treatment with a cytotoxic chemotherapeutic (170).

Keeping Prostate Cancer at Bay

Prostate cancer is the most commonly diagnosed cancer among men in the United States (10). It is also the second-leading cause of cancer death for U.S. men.

Most men who die from prostate cancer have metastatic disease. Thus, one goal of prostate cancer researchers is to identify new ways to increase the time before early-stage disease progresses and becomes metastatic. The molecularly targeted therapeutic apalutamide (Erleada)



266,120 new breast cancer cases
and
40,920 deaths
in U.S. women in 2018

2,550 new breast cancer cases
and
480 deaths
in U.S. men in 2018 (10).

recently became the first treatment approved by the FDA based on this outcome.

At the time of diagnosis, the growth of most prostate cancers is fueled by hormones called androgens. Androgens, such as testosterone, attach in a lock-and-key fashion to androgen receptors on individual prostate cancer cells, stimulating the cancer cells to multiply and survive. This knowledge led researchers to develop treatments that lower androgen levels in the body or stop androgens from attaching to androgen receptors. This approach to prostate cancer treatment is called androgen-deprivation therapy. It is an important part of care for many men with the disease.

Unfortunately, most prostate cancers that initially respond to androgen-deprivation therapy eventually begin to grow again. At this point they are said to be castration resistant.

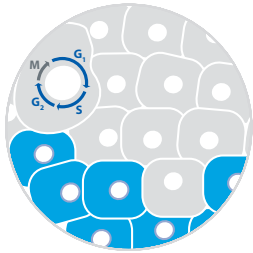
Even though the approaches to androgen-deprivation therapy that become the mainstay of prostate cancer treatment (bilateral orchiectomy or treatment with a gonadotropin-releasing hormone analog agonist or antagonist) reduce androgen levels in the body, they do not eliminate these hormones completely. Thus, castration-resistant prostate cancer growth is often fueled by androgens. Researchers, therefore, began developing a new generation of therapeutics that more effectively deprive prostate cancer of androgens. The first of these therapeutics, abiraterone (Zytiga) and enzalutamide

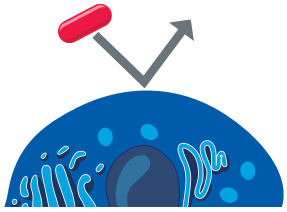
Biomarkers are cellular and molecular (including genetic and epigenetic) characteristics by which normal and/or abnormal processes can be recognized and/or monitored. They are measurable in biological materials such as tissues, cells, and/or bodily fluids.

THE CHALLENGE OF TREATMENT RESISTANCE

Diversity, or heterogeneity, among cancer cells within and between tumors is ultimately what leads to treatment resistance. Some examples of heterogeneity are as follows:

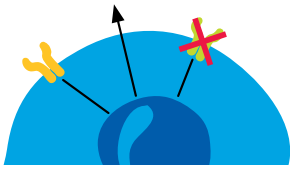
Not all cells in a tumor may be rapidly dividing; those that are not are insensitive to treatments targeting rapidly dividing cells such as cytotoxic chemotherapeutics.

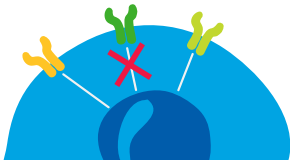




Some cancer cells in a tumor may have or may acquire mutations in the target of a given treatment that render the treatment ineffective.

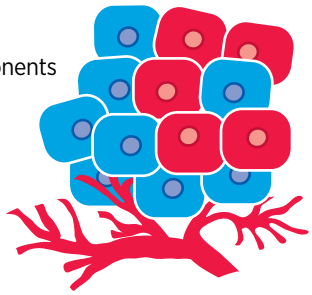
Some cancer cells in a tumor may have or may acquire molecular or cellular differences other than changes in the treatment target that render the treatment ineffective.





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

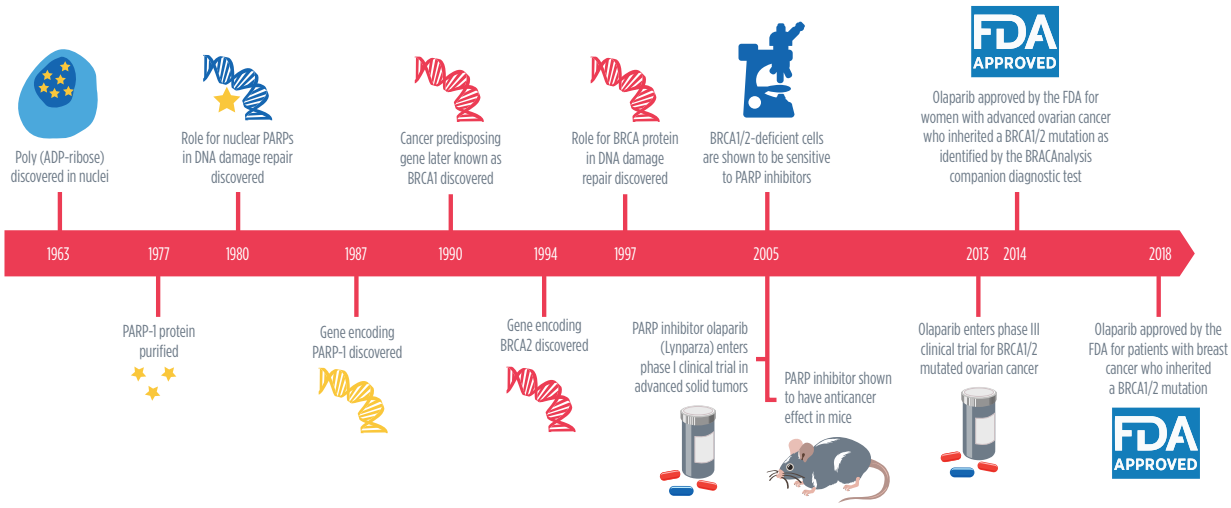
Differences in tumor microenvironment components can render a treatment ineffective.



Adapted from (1)

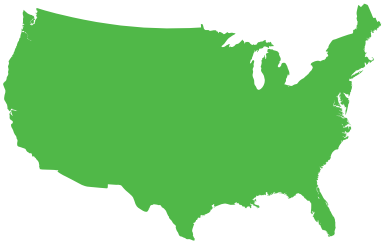
FIGURE 14

RESEARCH MILESTONES ON THE ROAD TO DEVELOPING OLAPARIB



Olaparib (Lynparza) is a molecularly targeted therapeutic that was approved for treating women with advanced ovarian cancer who have inherited a cancer-associated mutation in the BRCA1 or BRCA2 gene (BRCA1/2 mutation) in December 2014. In February 2018, it was approved for treating patients with HER2-negative, metastatic breast cancer who have inherited a cancer-associated BRCA1/2 mutation. Olaparib targets poly ADP-ribose polymerase (PARP) proteins. Five decades of basic and clinical research led to the development of olaparib, starting with the 1963 discovery that poly ADP-ribose could be generated by an enzyme in the nucleus. Other research milestones along the way to the FDA approvals include the purification of the PARP-1 protein, the discovery that PARP and BRCA proteins are involved in repairing damaged DNA, the discoveries of the PARP-1, BRCA1, and BRCA2 genes, and the demonstration that BRCA1/2-deficient cells and tumors are sensitive to PARP inhibitors. Data from (171, 172).

164,690 new prostate cancer cases



29,430 prostate cancer deaths

in the United States in 2018 (10).

(Xtandi), were approved by the FDA for treating men with metastatic castration-resistant prostate cancer in 2011 and 2012, respectively. Apalutamide is the first to be approved for treating men with nonmetastatic castration-resistant prostate cancer, such as **Ron Scolamiero** (see p. 78).

The February 2018 approval of apalutamide for treating men with nonmetastatic castration-resistant prostate cancer was based on results from a phase III clinical trial that showed that adding apalutamide to standard androgen-deprivation therapy increased the time before prostate cancer metastasized by more than two years (173).

Combining Molecularly Targeted Therapeutics

The first time the FDA approved the use of two molecularly targeted therapeutics as a combination treatment for cancer was January 2014 (1). The approval was for the use of dabrafenib (Tafinlar) and trametinib (Mekinist) for treating patients with metastatic melanoma that tests positive for certain mutations in the BRAF gene known as BRAF V600E and BRAF V600K mutations. The two therapeutics target different components of the BRAF signaling pathway. Dabrafenib targets BRAF proteins generated by BRAF

V600 mutations, while trametinib targets MEK1 and MEK2, which are two proteins that function further downstream in the BRAF signaling pathway. The combination was approved after it was shown to almost double the length of time before disease progression compared with dabrafenib alone (174).

In May 2018, this same combination of molecularly targeted therapeutics was approved for treating certain patients with a rare but highly aggressive type of thyroid cancer called anaplastic thyroid cancer. The combination of dabrafenib and trametinib was tested as a potential treatment for this type of cancer after genomic research showed that up to 50 percent of these cancers are fueled by BRAF V600 gene mutations (175). The approval, which is for the treatment of patients with BRAF V600E mutation–positive anaplastic thyroid cancer, was based on results from a phase II clinical trial that showed that treatment with dabrafenib and trametinib led to tumor shrinkage in more than 60 percent of the patients in a phase II clinical trial (175).

In June 2018, a new combination of therapeutics targeting the BRAF pathway was approved by the FDA for treating metastatic melanoma testing positive for a BRAF V600E or BRAF V600K mutation. Encorafenib (Braftovi) targets BRAF proteins generated by BRAF V600 mutations and binimetinib (Mektovi) targets MEK1 and MEK2. The approval was based on results from a phase III clinical trial, which showed that the time that patients had no disease progression was twice as long among those treated with the combination of encorafenib and binimetinib compared with those treated with vemurafenib (Zelboraf), which is another therapeutic that targets BRAF proteins generated by BRAF V600 mutations (176).

Treatment with Immunotherapeutics

Cancer immunotherapeutics work by unleashing the power of a patient's immune system to fight cancer the way it fights pathogens such as the virus that causes flu and the bacterium that causes strep throat. Not all immunotherapeutics work in the same way (see sidebar on **How Immunotherapeutics Work**, p. 80).

The use of immunotherapeutics in the treatment of cancer is referred to as cancer immunotherapy. In the past decade, it has revolutionized the treatment of an increasingly broad array of cancer types (see **Figure 15**, p. 81). In fact, a decade ago, on August 1, 2008, there were only four immunotherapeutics approved by the FDA and six types of cancer that could be treated by these agents. As of July 31, 2018, there were 19 immunotherapeutics approved by the FDA and one or more of these agents can be used to treat 19 types of cancer and to treat any type of solid tumor characterized by the presence of a specific molecular signature or biomarker.

One of the reasons that immunotherapy is considered one of the most exciting new approaches to cancer treatment that have ever entered the clinic is that some of the patients with metastatic disease who have been treated with these revolutionary anticancer treatments have had remarkable and durable responses, raising the possibility that they might be cured. 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 under way testing many novel immunotherapeutics and testing new ways to use those that we already have (177). 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, 2017, to July 31, 2018, and previously approved immunotherapeutics that were approved for use against additional types of cancer during the same period.

Boosting the Killing Power of the Immune System

Research has shown that immune cells called T cells are naturally capable of destroying cancer cells. It has also shown that in patients with cancer there are insufficient cancer-killing T cells, or the cancer-killing T cells that are present are unable to find the cancer cells or are unable to destroy the cancer cells for one of several reasons.

This knowledge has led researchers to identify several ways to boost the ability of T cells to eliminate cancer cells (see sidebar on **How Immunotherapeutics Work**, p. 80).

Anaplastic thyroid cancer

will account for **1–2%** of the 53,990 thyroid cancers projected to be diagnosed in the United States in 2018 (10, 175).

" **I hope that olaparib will be my miracle drug** and that I can continue to enjoy life with my family for a long time. "

CHOOSING TO ENJOY LIFE DESPITE METASTATIC BREAST CANCER

I was diagnosed with metastatic breast cancer in July 2015. I was totally devastated. But eventually, I decided that I was going to make the most of the time that I have with my husband and kids. I have been lucky that my treatments have let me do this. I am currently taking olaparib (Lynparza). It is controlling the tumors in my liver, which is the only place that I have active cancer right now. This is very exciting. I hope that olaparib will be my miracle drug and that I can continue to enjoy life with my family for a long time.

It all started three years ago. My husband and I were sitting out enjoying a nice summer evening when I felt stabbing pains in my right breast. I felt around and noticed a little hard knot on the underside of the breast.

The next morning, I called my gynecologist's office as soon as it opened. After seeing the doctor just 45 minutes later, I went straight for a mammogram and an ultrasound. I was told then and there that I probably had breast cancer.

A biopsy confirmed the news and showed that the cancer had spread to my lymph nodes. Even worse, a breast MRI and a PET scan revealed seven tumors in my right breast and tumors in my bones in five places. The diagnosis was stage IV, or metastatic, breast cancer. I was shocked. I was just 36, with two young children ages 6 and 3.

A few days after the diagnosis, I had surgery to remove my ovaries because they were the main source of the estrogen that was fueling the cancer. I also started taking letrozole, which blocks estrogen production, and palbociclib (Ibrance). This controlled my cancer for more than a year.

During that year, I underwent a double mastectomy, not to help me live longer but because I could feel the tumors in my breast. I also had genetic testing for inherited cancer-associated mutations because even though I had no family history of breast cancer I was very young to be diagnosed. I learned that I have a BRCA2 mutation that increases risk for several types of cancer, including breast cancer. This means my children have a 50 percent chance of having inherited this mutation, which is the hardest thing that I've had to deal with through all of this.

Unfortunately, after 15 months, a PET scan showed that a tumor in my hip was no longer responding to letrozole and palbociclib. I tried several other treatments but nothing stopped the cancer for long. It even spread to my liver.

In February 2018, I started taking olaparib. It is a PARP inhibitor, a targeted treatment that had only just been approved by the FDA for treating patients with breast cancer who have inherited a BRCA mutation. It is the first treatment that has made a difference since the cancer spread to my liver. My last scan, in June 2018, showed that two of the tumors in my liver are no longer active and that the third one is half as active as it was before.

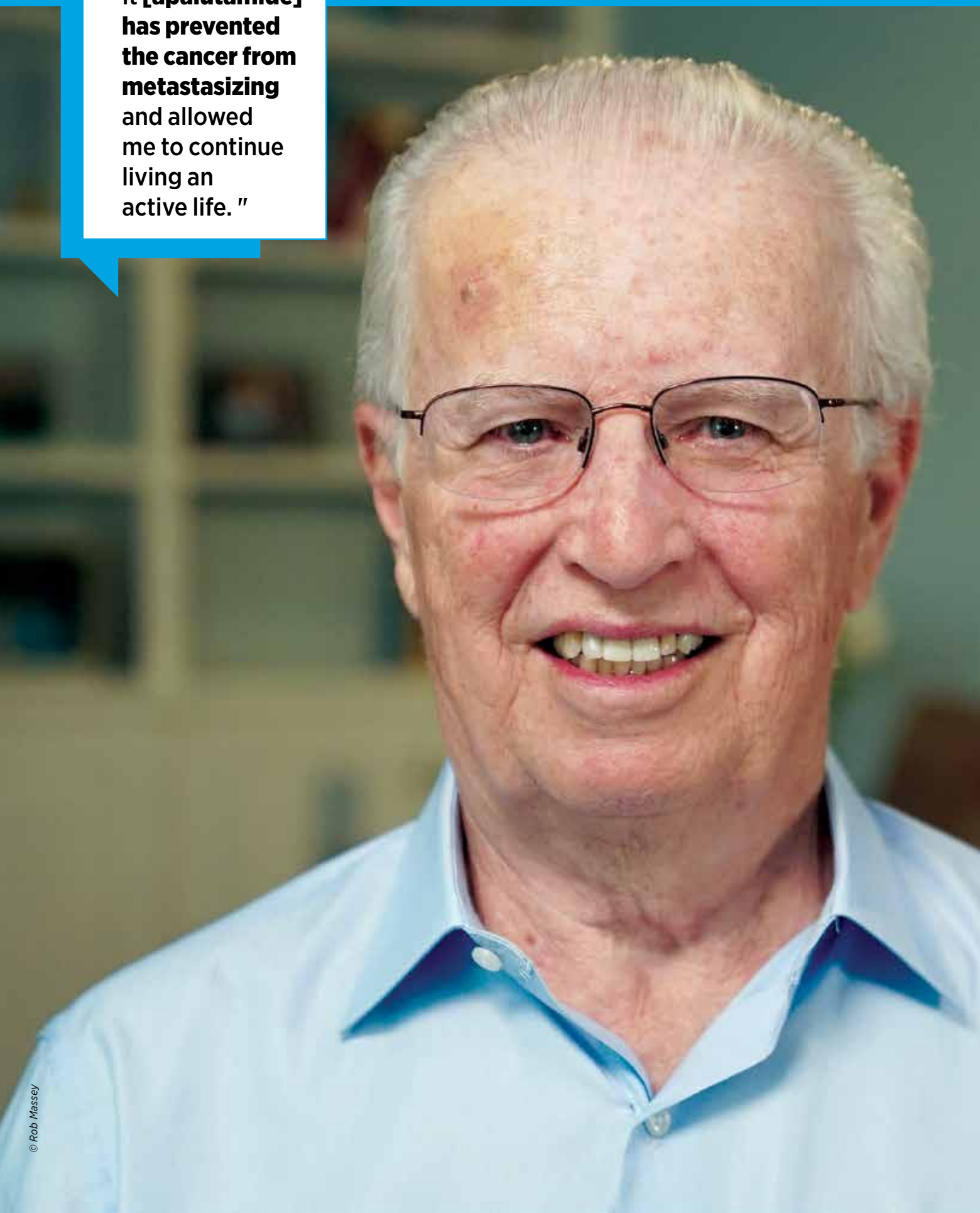
This is great news because I have been told that the only option I have after olaparib is chemo, unless new treatments come out. This makes me worry about the future. How long do I get with my children? How many birthdays do I get to see?

The worry affects my quality of life far more than physical side effects from treatment. At first, right after my diagnosis, I let my fears overcome me. I was very depressed and couldn't do anything. But then, after starting treatment and meeting other women with the same diagnosis in person and on social media, I decided that I couldn't let my fears stop me from enjoying life.

I chose to start living life again.

I love to go with my husband and kids to Springdale High School football games, the local pool, and my parents' house for Sunday dinners.

I am also dedicated to raising money for metastatic breast cancer research and to advocating for those of us with the disease. Funding for research is extremely important because it is the only way to develop new treatments that will keep those of us with metastatic cancer alive. We want to live. We want to see our children grow up. We want to know they will have a better chance of overcoming this disease than we do.


" It **[apalutamide] has prevented the cancer from metastasizing** and allowed me to continue living an active life. "

KEEPING METASTATIC PROSTATE CANCER AT BAY WITH APALUTAMIDE

Since I was diagnosed with prostate cancer 18 years ago, I have had several treatments. For the past 6 1/2 years, I've been receiving apalutamide (Erleada) through a clinical trial. It has prevented the cancer from metastasizing and allowed me to continue living an active life. I love boating, offshore fishing, golf, and spending time with my family and friends. None of this would have been possible without the research that led to the apalutamide clinical trial.

I was diagnosed with prostate cancer 18 years ago, when I was 55. The diagnosis was a complete surprise. It came about because I needed to take out a life insurance policy to complete a business deal. I was denied coverage because the physical exam revealed that I had a very high level of PSA.

The life insurance agent told me to see a urologist as soon as possible. A local urologist did a biopsy, which showed that I had prostate cancer. In delivering the news, the urologist told me that I had a maximum of five years to live. I was so numbed by the blunt assessment of my prospects that I drove by my exit on the highway several times on the way home.

After sharing the news with my immediate family, I set out to educate myself about the disease. At the time, it was extremely difficult to get health information on the Internet, so I wrote to the National Institutes of Health and several cancer organizations asking them to send me information. Wanting to keep my diagnosis private, especially for business purposes, I had the information sent to a post office box in a different town, which I rented especially for this mail. I was worried that people would think that it was a death sentence.

The urologist recommended immediate surgery. However, after seeking opinions from many prostate cancer specialists in Boston, I eventually decided on a combination approach to treatment. I took Lupron, which is a therapy that suppresses the production of hormones, and had a course of external-beam radiotherapy.

For about five years, it worked. There was no sign of prostate cancer. Then, the routine blood tests that I was having to monitor for a recurrence showed that my PSA levels were rising. After a period of watching my PSA levels slowly rise, I elected to have a salvage radical prostatectomy.

I was told that the surgery was my only shot at a cure. For about 12 months it seemed to be working; then, my PSA levels started rising again.

My doctors told me that the only thing they could offer me was the same hormone therapy but that it would not be a cure. Sure enough, my PSA levels rose gradually over the next few years. This was a difficult time for me. I was constantly worried that the prostate cancer would metastasize.

Fortunately, in 2012, one of the doctors in my medical team at Massachusetts General Hospital in Boston began a phase II clinical trial testing apalutamide. It was a new therapy designed to more effectively suppress hormones than the treatment I was on. I jumped at the chance to participate in the trial.

The apalutamide has pretty much controlled my prostate cancer for the past 6 1/2 years. In that time, the cancer has recurred locally, at the site where my prostate used to be. But these tumors have been removed through surgery. For the past two years, there has been no sign of cancer at all. I have a PSA test every 28 days, and a bone scan and CT scan every three months.

I am so grateful that I have been able to overcome all the speed bumps that prostate cancer has put in my way. There was a point after the salvage radical prostatectomy that my lifestyle was severely affected. The surgery had left me incontinent and I was unable to do very much for almost two years. Thankfully, my surgeon placed an artificial sphincter valve at the neck of my bladder that has enabled me to be continent and get back to living my life.

I feel very lucky that my cancer has been controlled by apalutamide. I know that research was critical to the development of this treatment that is making it possible for me to enjoy life. We need to put as many of our resources as possible into cancer research. It is the only thing that will allow us to one day find a cure.

One of the most recently developed ways to boost the killing power of T cells is through adoptive T-cell therapy (178). The goal of this approach to immunotherapy is to dramatically increase the number of functional cancer-killing T cells that a patient has. 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. 82).

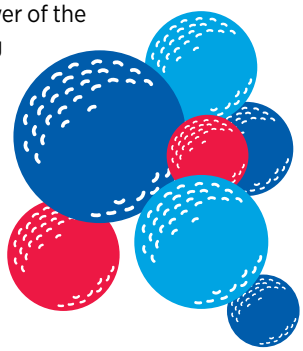
As of July 31, 2018, two of these revolutionary new types of immunotherapy had been approved by the FDA, axicabtagene ciloleucel (Yescarta) and tisagenlecleucel (Kymriah). Both are categorized as chimeric antigen receptor (CAR) T-cell therapy. Given that CAR T-cell therapy involves genetic modification of a patient's cells, it is sometimes referred to as cell-based gene therapy. For both axicabtagene ciloleucel and tisagenlecleucel, a patient's T cells are genetically modified to have a CAR that targets the molecule CD19.

HOW IMMUNOTHERAPEUTICS WORK

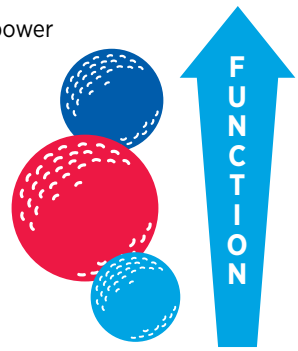
The ways in which different immunotherapeutics unleash a patient's immune system to fight cancer vary:

Some release the brakes on the natural cancer-fighting power of the immune system, for example, durvalumab (Imfinzi), nivolumab (Opdivo), and pembrolizumab (Keytruda) (see **Releasing Brakes on the Immune System**, p. 83).

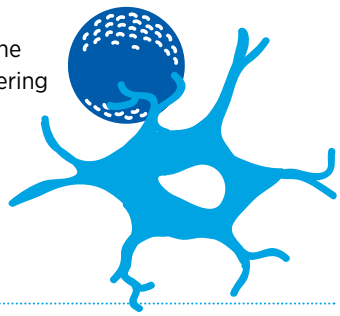
Some amplify the killing power of the immune system by providing more cancer-targeted immune cells called T cells, for example axicabtagene ciloleucel (Yescarta) and tisagenlecleucel (Kymriah) (see **Boosting the Killing Power of the Immune System**, p. 75).



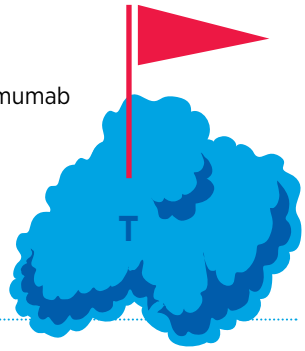
Some increase the killing power of the immune system by enhancing T-cell function, for example, interleukin-2 (Aldesleukin).



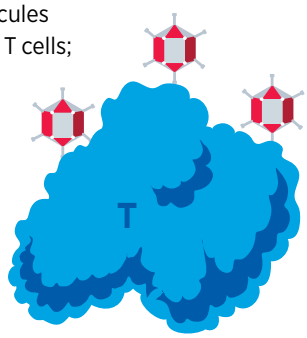
Some enhance the cancer-killing power of the immune system by triggering cancer-fighting T cells; these are called therapeutic cancer vaccines, for example, sipuleucel-T (Provenge).



Some flag cancer cells for destruction by the immune system, for example, daratumumab (Darzalex) and elotuzumab (Empliciti), which were highlighted in the *AACR Cancer Progress Report 2016* (36).



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), which was highlighted in the *AACR Cancer Progress Report 2016* (36).



Adapted from (1)

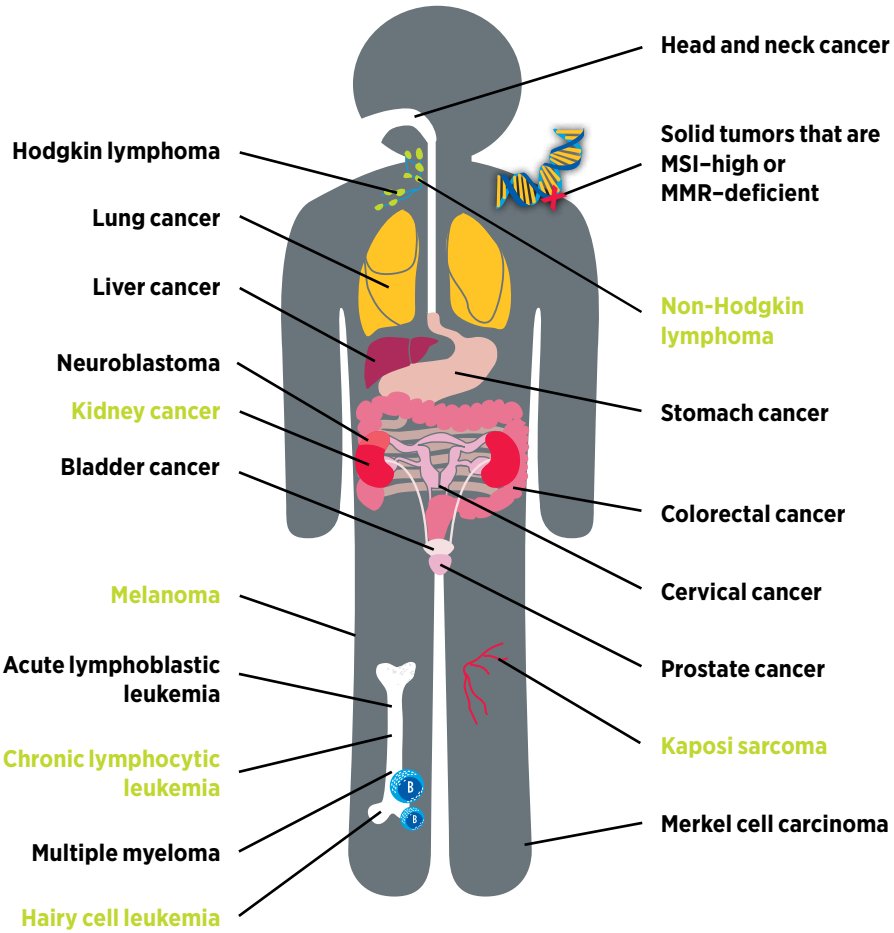
CD19 is a protein found on the surface of immune cells called B cells. Several types of leukemia and lymphoma arise in B cells, including most cases of ALL and most cases of non-Hodgkin lymphoma.

ALL is the most common cancer diagnosed among children ages 0 to 14 in the United States, with more than 3,000 new cases projected to be diagnosed in 2018 (10). In August 2017, tisagenlecleucel was approved for treating children and young adults up to the age of 25 with B-cell ALL that has not responded to standard treatments or has relapsed at least twice. The approval was based on results from a phase II clinical trial that showed that more than 80 percent of the children and young adults who were treated with tisagenlecleucel had remission within three months of receiving the CAR T-cell therapy (179). Results

FIGURE **15**

THE EXPANDING SCOPE OF IMMUNOTHERAPY

As of July 31, 2018,
immunotherapeutics were FDA approved for treating certain patients with:



Cancer immunotherapy refers to anticancer therapeutics that work by unleashing the power of a patient's immune system to fight cancer the way it fights pathogens such as the virus that causes flu and the bacterium that causes strep throat. In the 10 years since July 31, 2008, there has been a dramatic increase in both the number of immunotherapeutics approved by the U.S. Food and Drug Administration (FDA) and the number of uses for which they are approved. On August 1, 2008, one or more immunotherapeutics were approved for treating just six types of cancer (**shown in green**). As of July 31, 2018, one or more immunotherapeutics were approved for treating 19 types of cancer and for treating any type of solid tumor characterized by the presence of specific molecular characteristics, or biomarkers.

TYPES OF ADOPTIVE T-CELL THERAPY

There are three main types of adoptive T-cell therapy (178). As of July 31, 2018, only one type, chimeric antigen receptor (CAR) T-cell therapy, had been 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 (1)

from earlier, smaller clinical trials suggest that for some patients, like **Tori Lee** (see p. 84), remission following tisagenlecleucel treatment is durable, but further follow-up is needed to determine long-term overall survival rates (180).

In 2018, it is estimated that there will be almost 75,000 new cases of non-Hodgkin lymphoma diagnosed in the United States (10). The term non-Hodgkin lymphoma encompasses many different types of cancer. Two recent FDA decisions made axicabtagene ciloleucel and tisagenlecleucel approved treatment options for certain patients with non-Hodgkin lymphoma classed as large B-cell lymphoma, including diffuse large B-cell lymphoma (DLBCL), high grade B-cell lymphoma, and DLBCL arising from follicular lymphoma. Specifically, the CAR T-cell therapies are approved for those patients whose disease has not responded to or has relapsed after two other treatments.

The approvals of axicabtagene ciloleucel and tisagenlecleucel for large B-cell lymphoma, in October 2017 and May 2018, respectively, were based on results from phase II clinical trials (181, 182). In the axicabtagene ciloleucel clinical trial, more than 50 percent of the patients treated with the CAR T-cell therapy had complete responses, meaning that no cancer was detectable during at least one follow-up examination (181). In the other clinical trial, 32 percent of those treated with tisagenlecleucel had complete responses (182). Further studies are needed to determine whether axicabtagene ciloleucel and tisagenlecleucel improve overall survival. However, early results suggest that responses are durable for many patients (181, 182), providing new hope to patients like **Mike Delia** who was treated with axicabtagene ciloleucel in July 2016 (see p. 86).

Like all cancer treatments, CAR T-cell therapy can have adverse effects. Some of the adverse effects of CAR T-cell therapy can be very severe and, in some cases, life-threatening. One of the most concerning is cytokine-release syndrome. This can occur as the CAR-modified T cells attack the cancer cells because part of their job is to release substances called cytokines. In patients affected by cytokine-release syndrome, there is an overwhelming release of cytokines into the bloodstream, which can cause high fevers, flu-like symptoms, and a dramatic drop in blood pressure. For many patients, treatment with steroids can relieve the cytokine-release syndrome. However, others require treatment with tocilizumab (Actemra), which blocks a cytokine called IL-6. Tocilizumab had previously been approved by the FDA for treating several forms of arthritis, but was approved to treat severe or life-threatening cytokine-release syndrome caused by CAR T-cell therapy in August 2017. This approval highlights

how discoveries in one disease area can offer new ideas for the treatment of other diseases.

Given that CAR T-cell therapy can sometimes cause severe or life-threatening cytokine-release syndrome and other serious adverse effects, including potentially life-threatening swelling in the brain, the FDA has put in place a risk evaluation and mitigation strategy that requires that health care facilities using axicabtagene ciloleucel and tisagenlecleucel 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 (183-185).

In addition, several approaches to expand the utility of CAR T-cell therapy are already being tested in clinical trials, including evaluating T cells modified to have CARs that target proteins other than CD19 (178). For example, treatment with T cells modified to have a CAR targeting the molecule CD22, which is found on the surface of B cells, benefited some patients with B-cell ALL in a phase I clinical trial (186). In another phase I clinical trial, treatment with T cells modified to have a CAR targeting the molecule BCMA, which is found on some types of B cell, benefited some patients with multiple myeloma (187). However, these are preliminary results, and additional follow-up and clinical testing are needed to determine exactly how effective these CAR T-cell therapies will be.

Releasing the Brakes on the Immune System

Research has shown that one of the reasons that cancer-killing T cells present in a patient are unable to destroy the cancer cells is that some tumors have high levels of proteins that attach to and trigger brakes on T cells, stopping them from attacking. These brakes, which are on the surface of T cells, are called immune-checkpoint proteins.

This knowledge has led researchers to develop immunotherapeutics that release T-cell brakes. These immunotherapeutics are called checkpoint inhibitors.

Ipilimumab (Yervoy) was the first checkpoint inhibitor to be approved by the FDA, in March 2011. It targets the immune-checkpoint protein CTLA-4, protecting it from the proteins that attach to it and trigger it to put the brakes on T cells. Its approval for metastatic melanoma followed almost 25 years of basic and clinical research (see **Figure 16**, p. 88).

This was a landmark moment.

Ipilimumab was the first treatment ever to extend overall survival for patients with metastatic melanoma (196). In addition, the success of ipilimumab motivated researchers to focus on targeting other immune-checkpoint proteins.

Between September 2014 and May 2017, the FDA approved five other checkpoint inhibitors. These all release a different T-cell braking system compared with ipilimumab. 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. Nivolumab (Opdivo) and pembrolizumab (Keytruda) target PD-1, while atezolizumab (Tecentriq), avelumab (Bavencio), and durvalumab (Imfinzi) target PD-L1.

Since the initial approval of each checkpoint inhibitor, the FDA has expanded the number of cancer types for which they are approved. During the 12 months spanning this report, August 1, 2017, to July 31, 2018, the FDA expanded

The National Institutes of Health defines **gene therapy** as the use of genes to treat or prevent disease. Approaches to gene therapy can include:

1) Replacing a mutated gene that causes disease with a healthy copy of the gene.

2) Inactivating, or "knocking out," a mutated gene that is functioning improperly.

3) Introducing a new gene into the body to help fight a disease.

" There is no doubt in our minds that **CAR T–cell therapy**, and the research that led to it, **saved Tori's life.** "

BEATING LEUKEMIA THANKS TO CAR T-CELL THERAPY

A message from Chris and Dana Lee, Tori's parents

Our youngest daughter Tori was diagnosed with acute lymphoblastic leukemia (ALL) in October 2008. After four years of grueling chemotherapy and radiotherapy, the leukemia relapsed a second time. Fortunately, Tori was able to take part in a clinical trial testing a new type of treatment called CAR T-cell therapy. It is now more than five years since she received the treatment [now called tisagenlecleucel (Kymriah)] and she remains in remission. There is no doubt in our minds that CAR T-cell therapy, and the research that led to it, saved Tori's life.

Tori's diagnosis came just weeks after her fifth birthday. She had been having a lot of ear infections that required multiple courses of antibiotics. So, when she woke up one Saturday with all the symptoms of yet another ear infection, we took her to her pediatrician expecting nothing more than another prescription for antibiotics.

However, during the exam, the pediatrician felt that Tori's spleen was enlarged and did a rapid blood test. The results concerned the pediatrician enough to recommend that we go straight to the hospital for further tests.

At first, we had no idea what was wrong with Tori but we knew it must be bad; you don't get sent to the hospital on a Saturday unless it is serious. Then we started thinking about other symptoms Tori had been having—general exhaustion and unexplained vomiting. We began to be fearful that it might be leukemia. It was an excruciating two-day wait until the Monday, when a bone marrow biopsy confirmed our worst fears. Tori had ALL.

Tori began the standard treatment—six months of intensive chemotherapy followed by two years of maintenance chemotherapy—immediately. Unfortunately, Tori was a delayed responder, meaning the chemotherapy did not work as quickly as expected to eliminate the leukemia cells. This meant her treatment plan had to be lengthened, and she went through a year of very high-dose chemotherapy.

The chemotherapy was brutal. Tori had every side effect imaginable and was hospitalized many times.

Then, just before Tori was due to finish the maintenance therapy, when we thought it was nearly over and she was beginning to resume some activities, a routine spinal tap detected leukemia cells in her spinal fluid.

Tori had relapsed.

This time, Tori needed cranial radiation in addition to high-dose chemotherapy. Going through this second round of treatment was pure torture for us. There were moments when we didn't know if Tori would make it but she did, and her leukemia went into remission again.

Then, in November 2012, Tori relapsed for a second time. We were told that a bone marrow transplant was her only option. Her local oncologist recommended that we travel to Children's Hospital of Philadelphia (CHOP) for the procedure.

The oncologist at CHOP told us that to be eligible for a bone marrow transplant, Tori had to have more high-dose chemotherapy to get her into remission. She also told us that she had a back-up plan. The plan was to collect Tori's T cells before the high-dose chemotherapy so that if Tori did not get into remission she could take part in a clinical trial testing CAR T-cell therapy.

After the T cells were collected, and while Tori was beginning to prepare for a bone marrow transplant, we began researching the CAR T-cell therapy clinical trial. What we learned led us to ask the oncologists at CHOP if Tori could take part in the trial even if she got into remission. We felt CAR T-cell therapy would give Tori a better quality of life than a bone marrow transplant.

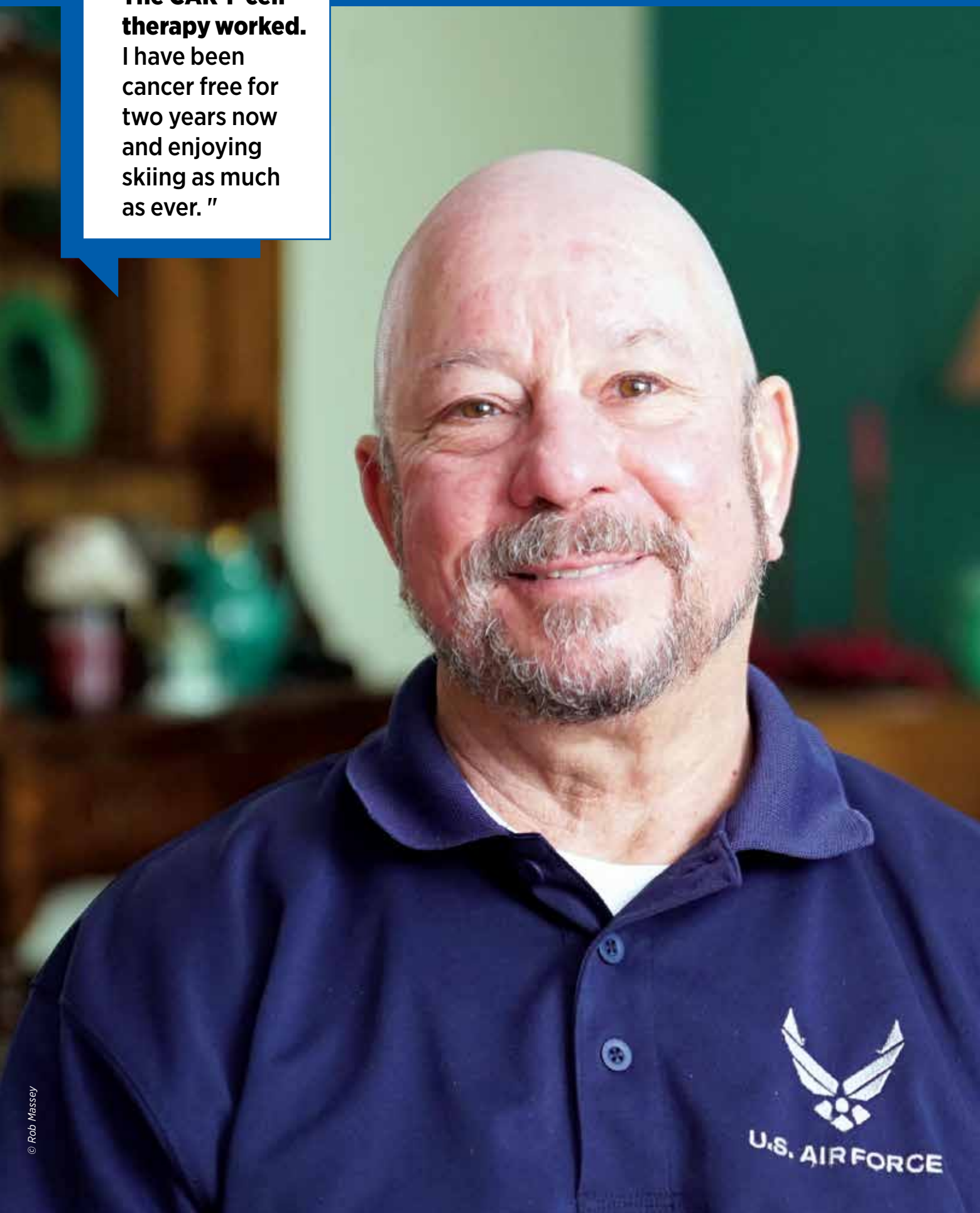
Thankfully, Tori entered remission and was accepted into the trial. She received the CAR T-cells in April 2013 and returned home five days later.

The difference between chemotherapy and CAR T-cell therapy was like night and day. The side effects of chemotherapy caused Tori to spend more than 300 nights in the hospital. The CAR T-cells were engineered to target the leukemia and Tori has not been hospitalized since she was discharged after the treatment.

Since receiving the CAR T-cells, there has been no sign of Tori's leukemia and she is living the life of a typical 14-year-old. She likes sports and going to the beach, and received a leadership award at her eighth-grade graduation.

Tori's experience has made us advocates for research into pediatric cancers. We want to do all we can to ensure that more money goes toward research because Tori is living proof of the amazing things that researchers can do.

" **The CAR T-cell therapy worked.** I have been cancer free for two years now and enjoying skiing as much as ever. "



SKIING WITH THE GRANDKIDS

THANKS TO CAR T-CELL THERAPY

In summer 2016, after my non-Hodgkin lymphoma relapsed for the third time, I chose to participate in a clinical trial testing a new immunotherapy. It was a CAR T-cell therapy now called axicabtagene ciloleucel (Yescarta). I chose this option because I felt that it was my only chance to get rid of the cancer for the rest of my life. Since receiving the treatment I've been cancer free, and earlier this year I fulfilled my dream of skiing in Sun Valley, Idaho, with my kids and grandkids.

I was diagnosed with large B-cell lymphoma, a type of non-Hodgkin lymphoma, in February 2014. However, I first noticed something was wrong the previous fall. I am an avid skier, and I was in the gym training for the upcoming ski season when I felt a lump in my right groin. My doctor initially thought I had aggravated a cyst. But after the lump grew from the size of a marble to the size of a small potato in less than four months, he sent me for a biopsy.

The biopsy showed that I had non-Hodgkin lymphoma. Then a CT scan revealed cancer not only in my right groin, but also in both lungs and in a couple of places on both sides of my lower back. This meant the non-Hodgkin lymphoma was stage III.

The diagnosis was a huge surprise because I didn't have any symptoms other than the lump, but I attribute it to being exposed to Agent Orange while serving as a helicopter pilot during the Vietnam War; I just can't prove it.

Despite the surprise, my initial reaction was, "Let's take care of it right away." I was convinced that I would beat it. I think that my military background—I finally retired as a full colonel from the U.S. Air Force in 1992—had a lot to do with this.

I opted to be treated here in Maine and started the standard treatment of chemotherapy and rituximab (Rituxan). However, I had a bad reaction to rituximab during the first infusion so I just continued with the cocktail of chemotherapy drugs. This seemed to work and I was free of cancer for a few months.

Unfortunately, in early 2015, the cancer relapsed in my right groin. More chemotherapy appeared to eliminate the cancer, but it returned in the same area in the summer of 2015. This time, radiation treatment seemed to clear the cancer, but it relapsed for the third time in early 2016.

Fortunately, my local oncologist was in communication with oncologists at the Dana-Farber Cancer Institute in Boston who were running a clinical trial testing a new CAR T-cell therapy for patients like me. The consensus recommendation was that I consider participating in the trial. Given that my other option was more chemotherapy, the decision to participate was a "no-brainer" for me.

The scariest thing about the trial to me was learning a whole new set of words, and understanding exactly how the treatment worked and what it would entail. I wasn't concerned about the treatment itself.

The first step of the treatment was leukapheresis, a process that allowed the Dana-Farber team to collect my T cells. The T cells were then sent to a laboratory in Santa Monica, California, where they were genetically engineered so that they would attack the cancer. Two weeks later, the engineered cells were infused into my body. I had to stay in the hospital after the infusion so the team could monitor me. I was lucky; I did not have any of the serious side effects that others have experienced with CAR T-cell therapy. The only thing I felt was extreme fatigue during the first two or three days after the infusion. By the fifth day I felt great, and by the eighth I went home.

The CAR T-cell therapy worked. I have been cancer free for two years now and enjoying skiing as much as ever. I don't know what the future holds because this treatment is so new. But I am hoping that it has conquered the cancer for the rest of my life.

I feel very fortunate to have participated in the clinical trial. It gave me the chance to be at the forefront of advances in cancer treatment. Funding for cancer research was key to the development of my treatment and I have confidence that with an infusion of more funds, we can surge forward and cure more people with cutting-edge new treatments.

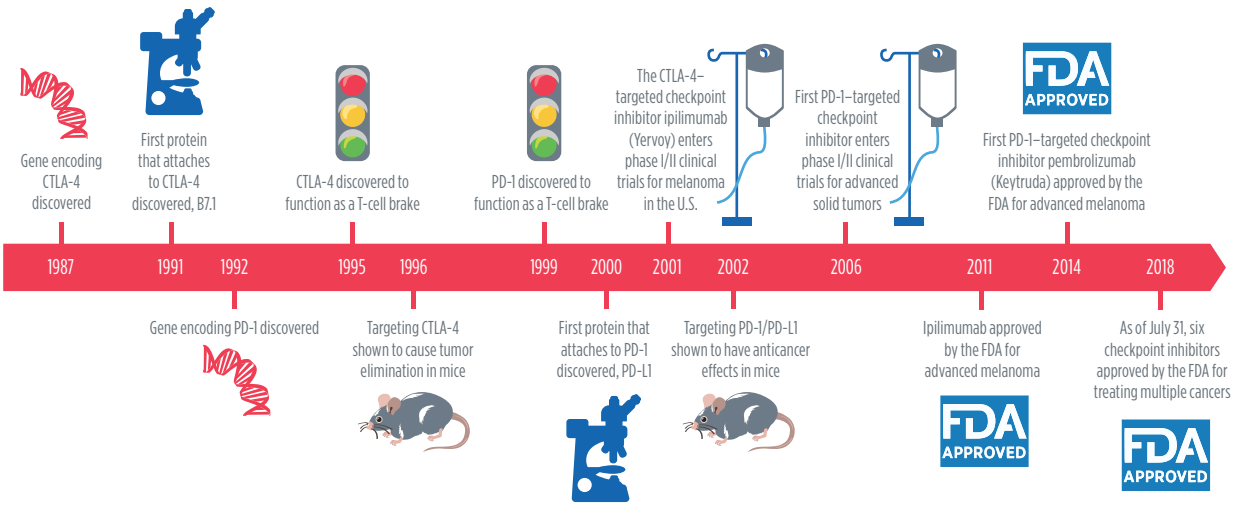
the uses of four of these immunotherapeutics—durvalumab, ipilimumab, nivolumab, and pembrolizumab—to include the treatment of additional types of cancer. These approvals mean that as of July 31, 2018, one or more checkpoint inhibitors were approved for treating 12 types of cancer and for treating any type of solid tumor characterized by the presence of specific molecular characteristics (see **Figure 17**).

One of the new types of cancer for which a checkpoint inhibitor is now an approved treatment option is hepatocellular carcinoma, which is the most common form of primary liver cancer (meaning cancer arising in the liver) to be diagnosed in the United States. In September 2017, nivolumab was approved for treating patients with hepatocellular carcinoma that has progressed despite treatment with the molecularly targeted therapeutic sorafenib (Nexavar), which is the standard treatment for the disease. The approval was based on results from a phase I/II clinical trial that showed that some patients had partial or complete tumor shrinkage after nivolumab treatment (197). Among those whose tumors shrank, the responses were durable, with most of them lasting 12 months or longer.

Another new type of cancer for which checkpoint inhibitors became an FDA-approved treatment is stomach cancer (gastric cancer). In September 2017, the FDA approved pembrolizumab for treating patients with recurrent locally advanced or metastatic, gastric or gastroesophageal junction adenocarcinoma that has progressed despite two other treatments and that tests positive for PD-L1 using a defined companion diagnostic (see sidebar on **Companion Diagnostics**, p. 67). The approval was based on the fact that pembrolizumab treatment led to tumor shrinkage in just over 10 percent of patients enrolled in a phase II clinical trial (198).

FIGURE **16**

STOPS ALONG THE WAY TO DEVELOPING CHECKPOINT INHIBITORS



Checkpoint inhibitors are cancer immunotherapeutics that work by releasing brakes 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. It targets a brake on T cells called CTLA-4. Several other checkpoint inhibitors target a second T-cell brake 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 (188, 189). Other basic research milestones along the way to the FDA approvals include the identification of the brake function of CTLA-4 and PD-1 (190–192), identification of the proteins that attach to and trigger the brake function of CTLA-4 and PD-1 (193, 194), and the demonstration that immunotherapeutics targeting these brakes can protect them from being triggered (189, 195).

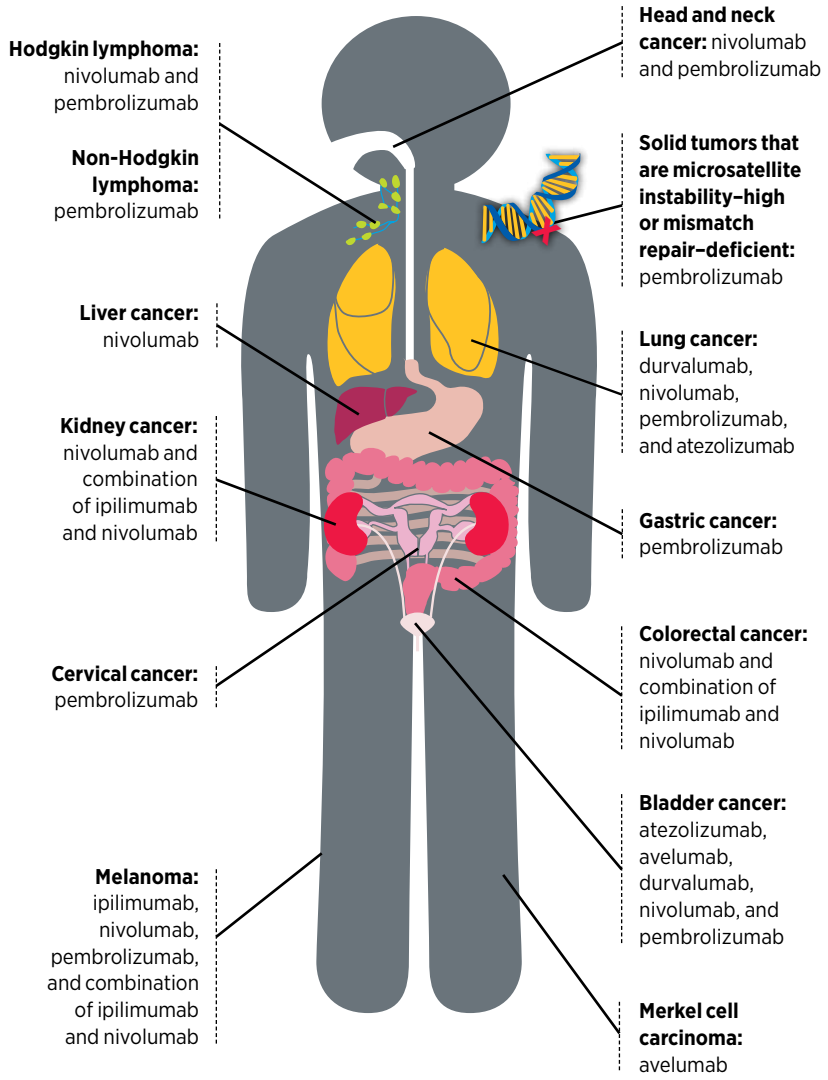
Adapted from (39).

In June 2018, the use of pembrolizumab was further expanded to include the treatment of certain patients with cervical cancer and certain patients with non-Hodgkin lymphoma. Specifically, pembrolizumab was approved for treating patients with recurrent or metastatic cervical cancer that tests positive for PD-L1 using a defined companion diagnostic and that has progressed despite treatment with cytotoxic chemotherapy, and for treating patients with primary mediastinal large B-cell lymphoma, which is an aggressive type of non-Hodgkin lymphoma, that has not responded to or has relapsed after two or more other treatments. The approvals were based on phase II clinical trial results showing that treatment with pembrolizumab led to tumor shrinkage in 14 percent and 45 percent of patients, respectively.

In addition, in August 2017, the FDA expanded the approved uses of nivolumab to include certain patients with colorectal cancer characterized by the presence of specific molecular characteristics, or biomarkers, called

FIGURE 17

GOING DEEP WITH CHECKPOINT INHIBITORS



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 four checkpoint inhibitors have been approved by the FDA, atezolizumab (Tecentriq), avelumab (Bavencio), 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, 2018, one or more checkpoint inhibitors were approved for treating 12 types of cancer and for treating any type of solid tumor characterized by the presence of specific molecular characteristics. 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 a treatment option.

Estimated New Liver Cancer Cases **42,220**

Estimated New Liver Cancer Deaths **30,200**

microsatellite instability–high and DNA mismatch–repair deficiency. Among these patients, nivolumab is intended for those whose cancer has progressed despite treatment with chemotherapy. The approval was based on results from a phase II clinical trial that showed that nivolumab treatment led to tumor shrinkage in more than 30 percent of patients (199).

The number of uses for which durvalumab is an FDA-approved treatment option was also expanded during the 12 months covered by this report. In February 2018, it was approved by the FDA for treating patients with stage III non–small cell lung cancer (NSCLC) whose cancer cannot be removed surgically and has not progressed after standard concurrent treatment with a platinum-based cytotoxic chemotherapeutic and radiotherapy. The approval was based on the fact that durvalumab treatment almost tripled the median length of time before disease progressed for patients enrolled in a phase III clinical trial (200).

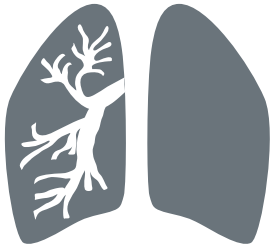
The successes with the five PD-1/PD-L1–targeted checkpoint inhibitors highlighted here have led to clinical trials in which these and other checkpoint inhibitors are being tested as a potential treatment for other types of cancer. Results are not available yet for most of these trials. However, initial results show that pembrolizumab may benefit some patients with mesothelioma (201), and that a new, investigational checkpoint inhibitor called cemiplimab may benefit some patients with cutaneous squamous cell carcinoma, which is the second deadliest skin cancer after melanoma (202).

Despite the tremendous achievements, treatment with FDA-approved checkpoint inhibitors yields remarkable and durable responses for only a minority of patients. Thus, researchers are testing various ways to increase the number of patients who benefit from these immunotherapeutics, including evaluating how well they work in combination. In May 2018, the FDA approved using ipilimumab in combination with nivolumab to treat certain patients with the most common form of kidney cancer, renal cell carcinoma. Among these patients, the combination is intended for those who have advanced renal cell carcinoma that is classed as of intermediate or high risk for a poor outcome with standard treatment with a molecularly targeted therapeutic such as sunitinib (Sutent). The approval was based on results from a phase III clinical trial that showed that the combination significantly improved overall survival rates compared with sunitinib (203).

In July 2018, the combination of ipilimumab and nivolumab was also approved for treating patients with colorectal cancer that is characterized by either the microsatellite instability–high or DNA mismatch–repair deficiency biomarker and that has progressed after treatment with a cocktail of cytotoxic chemotherapeutics. This approval was based on results from a phase II clinical trial that showed that 46 percent of patients who were treated with the combination had tumor shrinkage.

The idea of combining checkpoint inhibitors with immunotherapeutics that work in different ways, as well as with other types of anticancer treatments, including radiotherapy, cytotoxic chemotherapeutics, and molecularly targeted therapeutics, is also being tested in clinical trials for a wide array of types of cancer.

Another area of intensive research investigation is defining biomarkers that identify the patients most likely to benefit from a given checkpoint inhibitor. This is important



About **one-third of patients** with lung cancer have stage III disease at diagnosis.

because it could allow a patient unlikely to benefit to be spared the potential toxicity of the checkpoint inhibitor and to immediately start an alternative treatment. Currently, the presence of PD-L1 in a tumor and the presence of microsatellite instability–high or DNA mismatch–repair deficiency are used to identify the patients with certain types of cancer most likely to benefit from particular checkpoint inhibitors. However, these biomarkers do not work well for many types of cancer (204). Thus, there is an urgent need for new biomarkers. One showing early promise in a clinical trial evaluating nivolumab as a treatment for non–small cell lung cancer is high tumor mutational burden (205), but additional research is needed to determine how broadly this biomarker might be applicable before it can be used in the clinic.

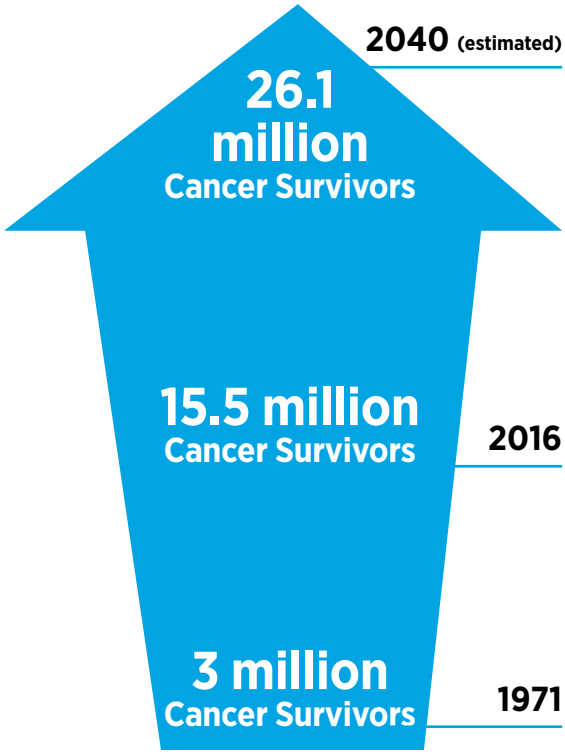
Supporting Cancer Patients and Survivors

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, as **Congressman Mark DeSaulnier** discovered after his 2015 diagnosis with chronic lymphocytic leukemia (CLL) (see p. 92). According to the latest estimates, more than 15.5 million U.S. adults and children with a history of cancer were alive on January 1, 2016, compared with just 3 million in 1971, and this number is projected to rise to 26.1 million by 2040 (206-208).

Each of these people has a unique experience and outlook, which can range from successful treatment and living cancer free for the remainder of his or her life to living continuously with cancer for the remainder of life. Therefore, not all people who receive a cancer diagnosis identify with the frequently used term "cancer survivor."

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. 94). Recent advances in cancer treatment were discussed in the previous three sections of the report (see **Treatment with Surgery, Radiotherapy, and Cytotoxic Chemotherapy**, p. 51, **Treatment with Molecularly Targeted Therapeutics**, p. 63, and **Treatment with Immunotherapeutics**, p. 75). Several of the advances highlighted in these sections are helping to reduce the short-term adverse effects of treatment as well as the long-term and late effects of treatment. Here, the discussion focuses primarily on other recent advances that can help improve outcomes and quality of life for individuals in each distinct phase of cancer survivorship.

Importantly, the issues facing each patient and survivor vary, depending on many factors, including gender, age at diagnosis, type of cancer diagnosed, general health at diagnosis, and type of treatment received. Recognizing that follow-up care for cancer patients can be complicated, the National Academy of Medicine recommends that after completing cancer treatment, every patient should be given a record of all the care he or she received and a tailored survivorship care plan that details the posttreatment care he or she needs to maintain or improve health and quality of life (209). For example, the survivorship care plan should include recommendations for cancer screening and the schedule on which it should be performed. However, survivorship care plans are not widely used, and more research is needed to determine how beneficial they are for



" I am dedicated to working with my congressional colleagues to **help more people live longer, higher quality lives after a cancer diagnosis.** "

COMMITTED TO HELPING MORE PEOPLE LIVE LONGER, FULLER LIVES AFTER A CANCER DIAGNOSIS

As a new member of Congress who received a cancer diagnosis six months after coming to Washington, D.C., my goal is to advance treatments and to help find a cure.In 2017, the National Institutes of Health (NIH) spent nearly $6 billion on cancer research. Federal investment in research has played a key role in making amazing advances that are extending and improving lives of patients and survivors. It is estimated that from 1991 to 2015 the overall death rate from cancer dropped by 26 percent, saving an estimated 2.4 million lives, largely due to improvements in cancer treatment, detection, and prevention.

This is progress that we can and must build upon. We need to continue to invest in cancer research, and improve both access to and the cost of lifesaving drugs, and enhance doctor-patient communications to help cancer patients and survivors from the moment of diagnosis through the rest of their lives as survivors.

I was diagnosed with chronic lymphocytic leukemia (CLL) in July 2015. It was a convoluted process. One day after a long run, I had a blood vessel pop in my eye. I went to a physician to have him look at it. While there, he suggested I should make an appointment with a dermatologist because he thought I should have an area of skin checked out. It was the dermatologist who noticed that my lymph nodes were enlarged and ordered the first blood tests that led to the diagnosis of CLL.

As someone who has always exercised and eaten healthily, I was shocked to learn I had CLL.

It took me a while to come to terms with the diagnosis, and it could have happened sooner with better doctor-patient communication. When you are in my generation and you hear the words, "You have cancer," you jump to conclusions that are not necessarily very healthy or accurate. Fortunately, an oncologist eventually said to me, "Mark, 15 years ago, if someone like you got your diagnosis, we would sprinkle some water on you and say, go and enjoy whatever time you have left. But with the treatments that we have available to us now, you can expect to live a normal lifespan."

My initial treatment was a chemotherapy infusion two days a month for six months. This eliminated the leukemia from my blood and I received no treatment for almost two years. At that time, there were signs the leukemia was returning and so I started taking an oral treatment, which I am still on.

Throughout the experience, I have been able to continue working and keeping my normal routine. Fortunately, I did not experience many of the physical side effects treatment can cause.

The emotional aspect of the diagnosis was harder, and gave me insight into the challenges faced by those who receive a cancer diagnosis.

A cancer diagnosis still carries a stigma. Despite disease being part of the human experience for thousands of years, we continue to stigmatize diseases like cancer. In doing so, we degrade our own humanity and put in place unnecessary obstacles that limit progress. Instead we should support efforts and investments that increase and extend the quality of life. In many ways the biggest obstacle we face in eradicating cancer is as much emotional as it is physical.

More and more people are living longer and fuller lives after a cancer diagnosis. We need to take every opportunity to increase public and congressional awareness about advances that have been made against cancer as a result of federal investment in the NIH, and highlight what more could be done if we increased federal funding for cancer research. For example, discoveries arising from NIH-funded research for cancer and other diseases have provided a foundation for the U.S. biomedical industry, which contributed $69 billion to our GDP.

Increasing federal funding for cancer research will allow us to achieve an important goal of the bipartisan Congressional Cancer Survivors Caucus that I recently formed with Congressman Ted Poe, which is to work toward a future in which more people beat cancer.

The Caucus is also working to identify ways to destigmatize cancer and to improve communication between physicians and patients. To this end, Congressman Poe and I recently introduced legislation—the Cancer Care Planning and Communications Act (H.R. 5160)—to help patients better navigate their cancer diagnoses.

As a cancer survivor, who is grateful to have a healthy and full life ahead of me, I am dedicated to working with my congressional colleagues to help more people live longer, higher quality lives after a cancer diagnosis.

LIFE AFTER A CANCER DIAGNOSIS IN THE UNITED STATES

When an individual becomes a cancer patient, 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.

Among the challenges experienced from the time from diagnosis to the end of initial treatment are (206):

choosing a physician(s) and treatment facility that are the right fit;

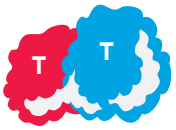
choosing among a variety of treatment options; and

managing adverse side effects of cancer and cancer treatment, many of which persist long term.

Many challenges experienced by cancer patients and survivors begin during cancer treatment and continue long term, but others can appear months or even years later. These long-term and late effects include, but are not limited to (206):

bone density loss (osteoporosis);

cognitive impairment, sometimes known as "chemo brain;"



diagnosis with a new form of cancer(s);

DISTRESS

distress, which can interfere with a person's ability to cope effectively with cancer and its treatment;

FATIGUE

fatigue that is severe and often not relieved by rest;

FEAR

fear of cancer recurrence;

heart damage (cardiotoxicity);

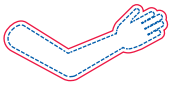
INFERTILITY

infertility (see sidebar on Preserving Fertility, p. 95);

lung (pulmonary) damage;

ENDOCRINE DYSFUNCTION

endocrine dysfunction (changes to the endocrine system, which is the collection of glands and organs that secrete hormones directly into the blood and lymphatic network);



lymphedema: swelling, most often in the arms or legs, that can cause pain and problems in functioning;

pain;

AGING

premature aging;

recurrence of original cancer; and

SEXUAL DYSFUNCTION

sexual dysfunction.

Although all cancer patients and survivors face challenges, survivors of cancer diagnosed from ages 0 to 19, during childhood and adolescence, 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)

patients and survivors to identify the best way to improve the quality of care and quality of life of cancer patients and survivors after they complete their treatment (210).

Individuals diagnosed with cancer during childhood or adolescence (ages 0–19) are particularly at risk for critical health-related problems because their bodies were still developing at the time of treatment. In fact, a recent study found that individuals who have been successfully treated for childhood cancer have experienced an average of 17 chronic health conditions by age 50, five of which were serious or disabling, life-threatening, or fatal (211). By comparison, individuals in the general population have experienced an average of nine chronic health conditions by the same age, only two of which are serious or disabling, life-threatening, or fatal.

Individuals diagnosed with cancer as young adults (ages 20–39) have the additional challenge of adapting to long-term cancer survivorship while beginning careers and thinking about starting families of their own (see sidebar on **Preserving Fertility**). Being proactive and talking to health care providers about the possible long-term and late effects of particular treatments before treatment begins can help some individuals identify ways to overcome the potentially life-altering effects of treatment, as it did for **Emily Bennett Taylor**, **Greg Aune**, and **Laurie Trotman** (see sidebar on **Looking Beyond Cancer Treatment**, p. 98).

Many treatments for cancer, including surgery, radiotherapy, and cytotoxic chemotherapy, can cause male and female infertility. Thus, parents of children and adolescents diagnosed with cancer, and adults, particularly young adults, diagnosed with cancer should consider discussing with their health care providers whether infertility is a risk for them and if it is, whether fertility preservation is right for them, and if it is, which fertility preservation option is best for them.

Unfortunately, certain segments of the U.S. population are disproportionately affected by the adverse effects of cancer and cancer treatment, which can negatively affect quality of life after a cancer diagnosis (see sidebar on **Disparities in Quality of Life after a Cancer Diagnosis**, p. 96). This disparity is not unique to the United States. In many developing countries, most patients and survivors receive no help in overcoming the physical, emotional, and psychosocial challenges that can occur as a result of a cancer diagnosis and treatment (212). For example, nearly all cancer patients in developing countries die with untreated pain, whereas this occurs very rarely in developed countries (212). Thus, it is imperative that all stakeholders in the global biomedical research community work together to address disparities in the care of cancer patients and survivors.

PRESERVING FERTILITY

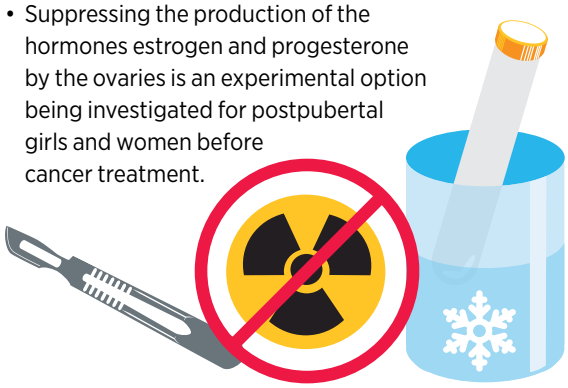
Many treatments for cancer, including surgery, radiotherapy, and cytotoxic chemotherapy, can cause male and female infertility. Thus, parents of children and adolescents diagnosed with cancer, and adults, particularly young adults, diagnosed with cancer should consider discussing with their health care providers whether infertility is a risk for them and if it is, whether fertility preservation is right for them, and if it is, which fertility preservation option is best for them.

Boys and Men

- Obtaining immature sperm or testicular tissue for banking is an experimental option being investigated for prepubertal boys before cancer treatment.
- Banking sperm is an option for postpubertal boys and men before cancer treatment.
- Shielding the testes from radiation is an option for boys and men during radiotherapy.

Girls and Women

- Obtaining ovarian tissue for banking is an experimental option being investigated for prepubertal girls before cancer treatment.
- Banking eggs is an option for postpubertal girls and women before cancer treatment.
- Banking embryos is an option for women before cancer treatment.
- Surgically moving the ovaries away from the part of the body receiving radiotherapy, a procedure called ovarian transposition, is an option for postpubertal girls and women before cancer treatment.
- Surgically removing the cervix but preserving the uterus is an option for women with early-stage cervical cancer.
- Shielding the ovaries from radiation is an option for girls during radiotherapy.
- Suppressing the production of the hormones estrogen and progesterone by the ovaries is an experimental option being investigated for postpubertal girls and women before cancer treatment.



It is not just cancer patients and survivors who are affected after a cancer diagnosis, but also their caregivers, and this population is growing proportionally with the number of cancer survivors. Caregivers are at risk for poor health outcomes, and this is often compounded by the fact that a subset of caregivers are already cancer survivors themselves.

Optimizing Quality of Life Across the Continuum of Cancer Care

One approach that can be used across the continuum of cancer care to optimize the quality of life for patients, survivors, and their families is palliative care (see sidebar on **What Is Palliative Care?** p. 97). 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 (215, 216). In addition, quickly integrating palliative care into the care that patients with serious illnesses such as cancer receive when hospitalized can significantly lower hospital costs (217). Thus, it is imperative that we increase awareness among both the general public and health care providers of the important role that palliative care can play across the continuum of clinical cancer care because there are still many patients who do not receive palliative care or even know what it is (218).

Preventing and Palliating Physical Symptoms

Preventing and palliating the physical symptoms and adverse effects of cancer and its treatment are becoming important because more and more people are living longer after a cancer diagnosis than ever before.

In January 2018, the FDA approved a new treatment for preventing bone complications in patients with multiple myeloma, the molecularly targeted therapeutic denosumab (Xgeva). In patients with multiple myeloma, the cancer cells accumulate in bone marrow—the soft, sponge-like tissue in the center of certain bones—which can damage and weaken the bone. Thus, bone complications, including bone pain and fractures, are adverse effects of the disease. Most patients are treated with bisphosphonates to help prevent bone complications arising. However, the use of these therapeutics is often limited by their adverse effects. Denosumab works in a different way from bisphosphonates to maintain bone density and strength. Its approval for preventing bone complications in patients with multiple myeloma was based on results from a phase III clinical trial (219). The results showed that it was as good as the bisphosphonate zoledronic acid in delaying the time to the first bone complication. Given that bone complications can be debilitating for patients with multiple myeloma, this approval provides a new option for maintaining their quality of life.

Acupuncture is a form of complementary medicine that has been shown to palliate some of the adverse effects of cancer and its treatment, and to improve quality of life for patients. For example, one recent study showed that acupuncture can reduce joint pain for postmenopausal women with early-stage breast cancer receiving treatment with an aromatase inhibitor (220). In another study, it significantly reduced the severity of insomnia among a group of cancer survivors clinically diagnosed with the condition (221). Other forms of complementary medicine

DISPARITIES IN QUALITY OF LIFE AFTER A CANCER DIAGNOSIS

Several segments of the population have been found to be disproportionately affected by the adverse effects of cancer and cancer treatment, which can negatively impact quality of life after a cancer diagnosis. Examples of these disparities include:

African-American women had a **two-fold increased risk** of breast cancer–related lymphedema (swelling in the arms that can cause pain and problems in functioning) compared with white women (213).

28% HIGHER

Adolescents and young adults surviving two or more years after a Hodgkin lymphoma diagnosis who lived in low socioeconomic neighborhoods had **28 percent higher** likelihood of respiratory system diseases compared with those in high socioeconomic neighborhoods (214).

WHAT IS PALLIATIVE CARE?

Palliative care is specialized care that provides an extra layer of support to patients with serious illnesses, such as cancer, and their families and caregivers.

It is not the same as hospice care, because it can be given throughout a patient's experience with cancer, beginning at diagnosis and continuing through treatment, follow-up, survivorship, and end-of-life care.

It can be given in addition to cancer treatment or to those with no curative treatment options; palliative care given near the end of life 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 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 (18)

have not been well studied, so we do not know if they are safe or effective. Thus, it is clear that there is an urgent need for more research in this area.

Psycho-oncology

A cancer diagnosis does not just pose physical challenges; it also poses behavioral, emotional, psychological, and social challenges. Researchers and health care practitioners working in the field of psycho-oncology are committed to developing new approaches to address these challenges, which include treatment-related cognitive impairment, fear of cancer recurrence, anxiety, depression, stress, and feelings of despair (see sidebar on **Helping Patients with Cancer Through Psycho-oncology Research**, p. 100). Addressing these challenges is important not just for improving quality of life, but also for improving outcomes because challenges such as depression and anxiety are often associated with decreased adherence to cancer treatment and decreased survival (222, 223).

According to the NCI, **complementary medicine** refers to treatments that are used alongside standard medical treatments but are not themselves considered standard treatments, for example, the use of **acupuncture** to help palliate some of the adverse effects of cancer treatment.

Modifying Behaviors to Improve Outcomes

Many factors related to lifestyle that increase a person's risk of developing cancer can also increase the risk of cancer recurrence and reduce survival time (see **Figure 3**, p. 25). In some cases, they have also been shown to increase a patient's risk of cancer treatment toxicity. Thus, modifying behaviors to eliminate or avoid these risk factors has the potential to improve outcomes and quality of life for cancer patients and survivors.

For example, recent research showed that men with localized prostate cancer who continue to smoke cigarettes during treatment are at higher risk of experiencing recurrence, metastasis, and death from prostate cancer (228). Fortunately, all cancer patients who are current smokers can improve their outlook by quitting smoking (52). Despite this knowledge, one study found that 9 percent of cancer survivors continue to smoke (229). Thus, more research is needed to develop optimal strategies to provide patients with cancer with the best chance of quitting smoking (230).

In recent years, evidence has emerged that regular aerobic exercise can reduce recurrence and mortality in survivors of several types of cancer, including early breast cancer, childhood cancer, colorectal cancer, and prostate cancer (231, 232). Evidence is also emerging that eating a diet rich in vegetables, fruits, and whole grains, or a diet high in fiber after a diagnosis of nonmetastatic colon cancer, can reduce mortality (233, 234). This evidence has largely come from observational studies. Determining if and how diet and exercise can be modified to improve outcomes for cancer survivors will require large, randomized, controlled studies. However, until definitive results from these are available, experts recommend that cancer survivors achieve and maintain a healthy body weight, participate in regular physical activity, and eat a diet rich in vegetables, fruits, and whole grains (235).

LOOKING BEYOND CANCER TREATMENT


© Dawn Bowery

EMILY BENNETT TAYLOR
AGE 34 • LOS ANGELES, CALIFORNIA

LIVING MY DREAM OF BEING A MOM

Throughout my treatment for stage IV lung cancer, the embryos that my husband and I had banked were a symbol of hope. They gave me the strength to get through the darkest days of treatment and I am so thankful to be a mom of two happy two-year-old girls.

My husband Miles and I were blindsided by my lung cancer diagnosis in June 2012; I was just 28. We couldn't believe that the future we had dreamed of might be taken away from us. Having children was a huge part of the dream so I set my heart on preserving sperm samples before my chemotherapy treatments began. Even though there were no facilities nearby, my doctor allowed us one week to explore opportunities for donation and banking.

With the help of family friends, my parents, located a facility in Seattle where I was able to bank four sperm samples. At the time, the doctors told us that current IVF methods were not very successful when previously frozen sperm was used to fertilize eggs. However, they foresaw scientific advancements enabling the use of frozen sperm to achieve viable pregnancies.

As predicted, technology did advance and our first cycle of IVF was successful when my wife became pregnant with twins. Noah and Emma were born in March 2003.

After two more rounds of IVF, my wife gave birth to our

TWENTY-EIGHT-YEAR CANCER SURVIVOR, PROUD DAD, AND SURVIVORSHIP RESEARCHER

As a 28-year survivor of Hodgkin lymphoma, I have experienced many late effects of cancer treatment, including infertility. Thanks to my mom discussing sperm donation with my pediatric oncologist, today my wife and I are blessed to have four amazing children that were conceived with in vitro fertilization (IVF).

I was diagnosed with Hodgkin lymphoma in December 1989, when I was just 16. After radiation did not eliminate the cancer, my parents and I were told I needed chemotherapy.

I'm incredibly fortunate that my mom had the foresight to ask the doctor if it was worthwhile for me to bank


© Dominique Moore

LAURIE TROTMAN
AGE 50 • HOOVER, ALABAMA

CHERISHING EVERY MOMENT WITH MY SON

Preserving my fertility before starting chemotherapy and radiotherapy gave me hope that there were better times ahead. Now I get to live those good times and I cherish every moment with my six-year-old son.

My diagnosis with stage IIB breast cancer in June 2008 changed my life. Not only did I have cancer, but I was also hit with the realization that I really wanted to have a baby one day. However, I was already 40, and my treatment plan not only included surgery, chemotherapy, and radiation, but also five years of tamoxifen to lower my

my fertility before starting treatment.

In the three weeks from the diagnosis to beginning chemotherapy, we underwent fertility treatment. The doctors harvested my eggs and after in vitro fertilization we had nine embryos that were frozen for future use.

The cancer treatments were extremely tough—numerous rounds of chemotherapy followed by a difficult surgery called an extrapleural pneumonectomy and 28 rounds of high-dose radiation—but they were successful. There has been no sign of cancer since I finished treatment more than five years ago.

Throughout treatment, I kept my focus on the future. Each day I would meditate, picturing scenes of a future with my husband and children: their first day of school, riding their bikes, celebrating their birthdays.

Two years after I completed the cancer treatment, we felt reasonably assured enough time had passed to start our family.

My doctors advised me that carrying and delivering a baby might be too much for my body. Fortunately, my high school track-and-field coach offered to be a surrogate. Our twin girls, Hope and Maggie, were born in April 2016.

The past two years have been a whirlwind but every day, I pinch myself. I am so lucky to be living my dream. ■

second set of twins, Elijah and Sophia, in April 2008.

Because of my mom's persistence and the work of countless scientists and physicians that has made technologies like IVF feasible for patients like me, my wife and I are blessed with four amazing children.

As a physician-scientist who cares for long-term pediatric cancer survivors, I see many patients who, unlike me, were not given the same opportunity to preserve their fertility. Because of my own experiences as a cancer patient and long-term survivor I have dedicated my scientific career to preclinical cancer survivorship research. Most importantly, I will always forcefully speak out on behalf of cancer survivors on the importance of adjusting the culture of cancer care to focus on both survival and long-term quality of life. ■

GREG AUNE, MD, PHD
AGE 45 • SAN ANTONIO, TEXAS

risk of the cancer returning. What chance did I stand of having a baby after all that was done?

I decided to explore the possibility of fertility preservation. After consulting a specialist, I had 14 viable eggs frozen and stored in the six weeks between having a lumpectomy and starting chemotherapy and radiation. Before the procedure, I remember the anesthesiologist telling me, "We'll save your eggs for a better time." His words resonated with me, and knowing that I had eggs frozen away was a ray of hope throughout chemotherapy and radiotherapy.

After lots of soul searching and deep conversations with my sister and a woman in a similar situation—a single, hard-working professional going through breast cancer treatment who had undergone fertility treatment—I decided to put aside my fears of the cancer recurring and go ahead with my plan to become a mom.

After about 18 months of tamoxifen, I took a break from the treatment to try in vitro fertilization of my frozen eggs with donor sperm.

The first attempt to get pregnant failed but the second was successful and I gave birth to my son, Tristan, on April 5, 2012.

Having Tristan is the most amazing thing that ever happened to me. Every day, I take time to remember how lucky I am to have him and to continue to be cancer free. ■

HELPING PATIENTS WITH CANCER THROUGH PSYCHO-ONCOLOGY RESEARCH

Health care practitioners working in the field of psycho-oncology, including psychiatrists, psychologists, and nurses, are dedicated to addressing the behavioral, emotional, psychological, and social challenges faced by patients with cancer. Examples of recent psycho-oncology clinical trials investigating new approaches to helping patients with cancer follow:

A **psychoeducational intervention** called ConquerFear comprising five sessions with a psychologist or psychiatrist reduced fear of cancer recurrence among survivors of breast cancer, colorectal cancer, and melanoma (224).

A **blended cognitive behavior therapy** involving five 1-hour sessions with a psychologist combined with three 15-minute e-consultations reduced fear of cancer recurrence among survivors of breast cancer, prostate cancer, and colorectal cancer (225).

A **web-based stress management program** called STREAM improved quality of life and reduced distress among patients newly diagnosed with cancer who were receiving their initial treatment (226).

An **Internet-based cognitive behavioral therapy** involving about 20 weekly sessions with a psychologist or sexologist improved sexual functioning, body image, and menopausal symptoms among breast cancer survivors diagnosed with a sexual dysfunction (227).

LOOKING TO THE FUTURE

IN THIS SECTION, YOU WILL LEARN:

- Innovations in science and technology across the spectrum of cancer research will shape the future of clinical cancer care.
- Integration and mining of health care data from various sources will allow researchers to gain more insights into cancer biology and thereby improve patient outcomes.
- Liquid biopsies have the potential to transform early detection, diagnosis, and treatment of cancer in the future.
- Examining the gut microbiome will augment our understanding of cancer development and may provide an exciting new avenue to improve cancer treatment.

This is an incredibly exciting era for cancer research. Approval of novel therapeutics, coupled with an increasing public awareness of cancer prevention and early detection, has contributed to improved outcomes and dramatic reductions in mortality rates for several cancers over the past decade. Despite these advances, cancer continues to be an enormous public health challenge in the United States and worldwide (see sidebar on **Cancer: A Global Challenge**, p. 11). In fact, it is predicted that 609,640 people in the United States will die from some type of cancer in 2018. However, many researchers, including **AACR President, 2018–2019, Elizabeth M. Jaffee, MD**, are extremely hopeful about the future because they are confident that research will power more advances against cancer (see p. 104).

One way to accelerate the pace of progress, among others, is to increase collaboration between cancer researchers and experts from other disciplines such as mathematics, physics, chemistry, engineering, and computer science. The new wave of innovations driven by convergence science will have a transformative impact on future progress across the clinical care continuum.

Convergence science is the convergence of the life sciences with fields including physical, chemical, mathematical, computational, engineering, and social sciences to tackle complex challenges and achieve new and innovative solutions (236).

HARNESSING PATIENT DATA TO IMPROVE OUTCOMES

To achieve the full potential of precision medicine, the molecular characteristics of a patient's cancer need to be considered along with other factors, such as the patient's genome, epigenome, microbiome, metabolome, lifestyle, and environmental exposures, all of which are emerging as important influences on cancer initiation, development, and progression.

Big Data

Integrating and harnessing data that include patient history, diagnostics, genetic tests, treatment decisions, and measured and patient-reported outcomes from large numbers of cancer patients may help answer many of cancer's most elusive questions in real time. For example, physicians may be able to match existing FDA-approved molecularly targeted therapeutics to novel cancer types, as well as to identify subgroups of patients who are most or least likely to benefit from aggressive therapies.

Several cancer organizations as well as multi-institutional teams have already launched a number of initiatives to catalyze data integration. A few examples of these cross-institutional projects are NCI Genomic Data Commons, BRCA Exchange, ASCO CancerLinQ, Oncology Research Information Exchange Network, and AACR Project Genomics, Evidence, Neoplasia, Information, Exchange (GENIE) (237).

Digital Health Platforms

Collection of patient-reported outcomes (PROs) enables direct measurement of the experiences of patients with cancer. Until recently, PROs have primarily been captured through surveys whereby patients fill out questionnaires to report symptoms (238, 239). However, innovative methods to document PROs, captured through wearable devices or mobile apps on smartphones, are increasingly providing a critical new perspective on clinical research and patient-centered care. Detailed information about symptoms, treatment burden, quality of life, and other experiences, documented in real time, is anticipated to provide researchers with a vast amount of previously untapped "big data" that can be harnessed for patient benefit. For example, symptoms monitored in real time can alert health care professionals to problems that might require immediate attention leading to modifications in treatment or even designs of clinical trials.

A NEW WAVE OF TECHNOLOGIES

The next generation of therapeutic and diagnostic technologies that are moving rapidly from the bench to the bedside has the potential to fundamentally change cancer treatment in the future.

Artificial Intelligence

As we accumulate large quantities of cancer patient data, artificial intelligence (AI) approaches, such as machine learning or "deep 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. Machine learning is an application of artificial intelligence (AI) that focuses on the development of computer programs that can access and use data to learn for themselves.

A critical step in diagnosing cancer is pathology testing, which involves a pathologist's viewing a slide on which there is a slice of the abnormal tissue, obtained through tissue biopsy or during surgery, under a conventional light microscope to determine the size, shape, and appearance of the tissue and the cells. The application of AI in pathology testing is an area of extensive research. AI has the potential to streamline processes for image interpretation from pathology slides as well as many other image sources that are routinely used in oncology, allowing for faster decision-making for people with life-threatening diseases. A digital pathology system called IntelliSite Pathology Solution was approved by the FDA in April 2017 (highlighted in the *AACR Cancer Progress Report 2017*). Continued research is needed to determine the full clinical potential of AI, along with appropriate regulatory approaches to ensure safety and efficacy of these novel technologies (240-242).

Gene Editing Using CRISPR

Investigating the effects of changing, or editing, the genetic material of a cell is an important part of biomedical research. CRISPR is a revolutionary approach to gene editing that has emerged recently (243). It provides a faster and more precise and efficient approach to gene editing compared to previous technologies. The development of CRISPR technology was based on basic research into the immune system of certain species of bacteria. CRISPR technology is being currently used by researchers throughout the biomedical research community in numerous ways. One area of extensive investigation is to identify safe and effective ways to use CRISPR-mediated gene editing for cancer therapy (244).

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 the course of

In June 2016, the FDA approved the first **liquid biopsy companion diagnostic test** for identifying whether or not a patient with metastatic non–small cell lung cancer is eligible for treatment with the EGFR-targeted therapeutic erlotinib.

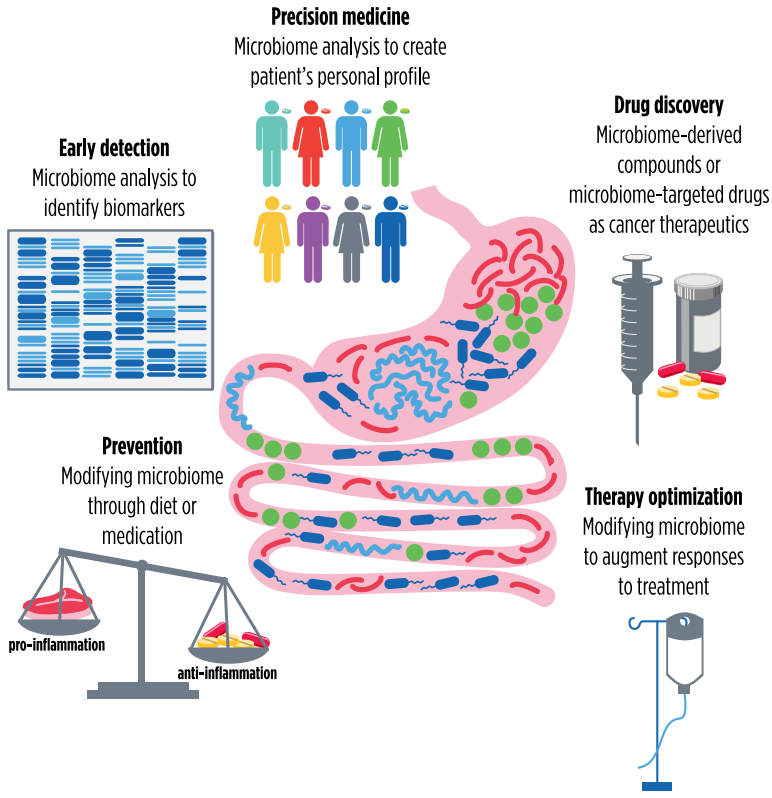
cancer development and treatment, tumors routinely shed detectable cells, lipid-encapsulated sacs called exosomes, as well as free DNA into a patient's blood (see sidebar on **Moving toward Minimally Invasive Testing**, p. 106). Recent studies have shown that it is possible to use a blood sample, or liquid biopsy, rather than a traditional tissue biopsy, to obtain material that can be analyzed to provide information about the molecular alterations associated with a patient's cancer (245, 246). Liquid biopsies have the potential to transform early detection, diagnosis, treatment, and surveillance of cancer by identifying markers of disease, therapeutic response, resistance, and recurrence.

MICROBIOME AND CANCER

The human body contains trillions of microbes from many different species of bacteria, fungi, parasites, and viruses that reside in multiple sites such as the skin, eyes, mouth, digestive system, and genitals. The microbiome is defined by the NCI as the collection of all the microorganisms and viruses that live in a given environment of the human body. The gut microbiome has become an exciting new area in biomedical science, both for understanding cancer development and progression, and as a novel therapeutic modality (see **Figure 18**).

FIGURE **18**

THE GUT MICROBIOME: UNCOVERING NEW AVENUES FOR CANCER PREVENTION, EARLY DETECTION, AND TREATMENT



The gut microbiome is an exciting new area in cancer research. Investigations are under way to study whether it is possible to harness the human gut microbiome to prevent, detect, diagnose, or optimize cancer treatment. Manipulating the microbiome through lifestyle modifications such as changes in diet, might aid in cancer prevention by suppressing chronic inflammation, while detection of certain microbial species that are frequently associated with cancer incidence may help in early detection or diagnosis of disease. The gut microbiome may also have a dramatic impact on the efficacy of anticancer immunotherapies and chemotherapies. Manipulating the microbiome in cancer patients through advanced probiotics, fecal transplantation, or pharmacologic interventions may open up new opportunities to improve patient outcomes and further precision medicine.

" **Enlisting experts from an even broader spectrum of disciplines,** including physics, chemistry, engineering, mathematics, and computer science, will significantly accelerate the pace of progress in the future. "

ELIZABETH M. JAFFEE, MD • AACR PRESIDENT, 2018–2019
Deputy Director, The Sidney Kimmel Comprehensive Cancer Center
at Johns Hopkins University, Baltimore, Maryland

ENVISIONING LONGER, HIGHER QUALITY LIVES FOR CANCER PATIENTS

During the almost 30 years since I began my fellowship in oncology, we have made unprecedented progress against cancer. These advances occurred largely because of tremendous progress in basic research. A continued increase in federal funding for both basic and clinical research will allow us to make major headway moving forward. We will be able to develop cures for more cancers, as well as new treatments that will convert metastatic cancers from deadly to chronic diseases for many more patients.

When I first started my career, we had very few good treatments. A diagnosis with metastatic cancer was almost always a death sentence. Cancer care has evolved rapidly, and now there are treatments that result in responses that last years for some metastatic patients. For these patients, we can think of cancer as a chronic disease that needs to be controlled much like diabetes and cardiovascular disease.

Immunotherapy is a great example of how tremendous progress has been made because of basic research. Many of the recently approved immunotherapeutics—the checkpoint inhibitors and CAR T-cell therapies—work by altering immune cells called T cells, which can recognize and kill cancer cells. We were able to develop these new treatments, which are yielding durable responses for some patients, because of decades of basic research that taught us about T cells and how they are activated and regulated.

I believe that to advance cancer research even further, we must increase the integration of researchers from diverse disciplines into the cancer field. Bringing together researchers from a wide array of disciplines to address a single complex disease, such as cancer, is referred to as convergence science.

We have already seen that the convergence of immunotherapy and genetics has brought the concept of precision oncology to immunotherapy with the recent approval of an immunotherapeutic for treating any type of solid tumor characterized by a specific genetic characteristic, or biomarker. Enlisting experts from an even broader spectrum of disciplines, including physics, chemistry, engineering, mathematics, and computer science, will significantly accelerate the pace of progress in the future.

Convergence science will also help drive new technologies from the bench to the bedside. For example, technologies such as liquid biopsies have great potential for transforming early detection, diagnosis, and treatment of cancer by identifying markers of disease, therapeutic response, resistance, and recurrence. However, we need to improve the precision of these technologies before they can become a standard part of cancer care for most patients.

Another way that new technology will shape the future of cancer research and care is through a field of computer science called machine learning, which involves using small sets of data to develop programs that allow us to draw inferences about larger populations of patients with similar characteristics. Other areas of computer science will also be key to integrating and harnessing large sets of patient data, including patient history, outcomes, and tumor genetics, to expedite progress in precision oncology.

Because recent research findings are allowing more people to survive longer after a cancer diagnosis, one area in which we will see advances in the near future is in the identification of ways to minimize the risks of short- and long-term side effects from cancer treatment. We need to ensure that the new treatments we develop confer maximal benefit and minimal risk. We also need to ensure that we are using current therapeutics in ways that give patients the best possible quality of life for the long term.

I foresee a future in which a patient with cancer, even one with metastatic disease, would visit his or her oncologist periodically during which the patient might receive a treatment or have the treatment regimen tweaked. The cancer would be under control, and it will be possible for the patient to live a normal life.

If we are to realize this bright future for cancer patients and survivors, we need robust annual increases in federal funding for research. These resources are vital if we are to achieve our goal of bringing research advances against cancer to all Americans.

A potential role of the gut microbiome in cancer development has been suggested in several recent studies. For instance, the presence of certain bacterial species was reported in the guts of individuals with familial adenomatous polyposis (FAP), an inherited genetic condition that almost inevitably leads to colon cancer (see **Table 3**, p. 20) (247). Further investigation revealed that these bacteria release toxins that can damage the DNA of colon cells, which may lead to cancer development. Future studies will examine whether early detection and manipulation of specific microbes in the gut may aid in cancer prevention or interception.

Emerging evidence suggests that the gut microbiome may also play a critical role in determining responses to cancer therapy. Certain intestinal microbes can in fact break down cancer chemotherapies, rendering them ineffective or even toxic (248, 249). In addition, gut microbes can significantly influence the host immune system and potentially impact the effectiveness of cancer immunotherapies (250, 251). Ongoing and future research will identify innovative approaches to harness the gut microbiome for the discovery of diagnostic and therapeutic tools in cancer.

MOVING TOWARD MINIMALLY INVASIVE TESTING

Liquid biopsy refers to the collection and analysis of biofluids, such as blood or urine. In oncology it primarily involves the capture and analysis of cells, lipid-encapsulated sacs called exosomes, or free DNA shed by tumors into the blood. For example, a blood sample, rather than a biopsy of the tumor tissue itself, could be used to analyze genomic alterations in a patient's cancer. Currently, many liquid biopsy platforms are being developed and tested. The major advantages compared to traditional tissue biopsies are:

- Liquid biopsies have the potential to be safer, quicker, more easily obtainable, more likely to result in patient compliance, and better representative of tumor heterogeneity than a typical biopsy.

- Liquid biopsies provide minimally invasive ways to detect early evidence of disease, monitor minimal residual disease, and repeatedly sample the genomes of different tumor lesions to evaluate whether a cancer is responding to treatment or becoming treatment resistant and, if it is developing resistance, determine what treatment might be the most appropriate next option.

Ongoing research will continue to evaluate the clinical utility of these approaches.

WORKING TOGETHER TO OVERCOME CANCER THROUGH SCIENCE-BASED, PATIENT-CENTERED PUBLIC POLICY

IN THIS SECTION, YOU WILL LEARN:

- Federal funding for biomedical research, most specifically through NIH and NCI, has a significant impact on our nation's health and the United States economy.
- Regulatory science initiatives at the FDA are vital to accelerating 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 significantly reduce cancer risk.
- Newly passed legislation aims to improve outcomes for children and adolescents who are diagnosed with cancer.

There has never been a time of greater excitement in cancer research. The rapid pace of progress and the broadening scope of the advances made in recent years have been extraordinary. As detailed in **Cancer in 2018** (see p. 7), the hard work of individuals from all segments of the biomedical research community continues to transform the way we prevent, detect, diagnose, and treat cancer. Despite the progress, however, cancer remains a formidable challenge; it will claim an estimated 609,640 lives in the United States in 2018 (10).

Fortunately, scientific opportunities now exist that were previously unimaginable and that hold great promise for achieving our ultimate goal of preventing and curing all cancers.

To seize the opportunities that lie before us, and meet the challenges ahead, we need robust, sustained, and predictable funding for biomedical research through the NIH. For the research investments to yield dividends in the form of new medical products and community-based programs to improve public health, we also need strong federal investments in agencies such as the FDA and the CDC, and evidence-based policy making across and throughout the biomedical research ecosystem (see sidebar on **Building Blocks to Overcome Cancer Through Science Policy**, p. 107).

MAINTAINING THE MOMENTUM WITH CONTINUED ANNUAL FUNDING INCREASES FOR BIOMEDICAL RESEARCH

Federal funding through the NIH is the lifeblood of biomedical research. It forms the foundation upon which most scientific discoveries in the United States are made. Faithfully investing federal dollars in biomedical research over many years can yield tremendous dividends. Many of the major medical breakthroughs made in the last 50 years can be traced in large part back to an NIH grant, including the extraordinary progress detailed in this report. Moreover, a recent study found that NIH funding contributed to the development of 210 new molecular entities approved by the FDA between 2010 and 2016 (24).

The AACR is deeply grateful to U.S. House and Senate leaders for making medical research a national priority in recent years and for working in a bipartisan way to set the NIH and NCI back on paths of annual growth above medical inflation (see **Figure 19**, p. 109). Since fiscal year (FY) 2015, Congress has renewed its commitment to the promise of biomedical research and increased the NIH

BUILDING BLOCKS TO OVERCOME CANCER THROUGH SCIENCE POLICY

To accelerate the pace of progress against cancer, we must:

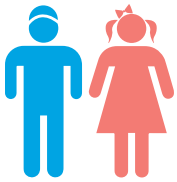
Sustain annual increases in federal funding for biomedical research, including support for a vibrant research workforce.

Support regulatory science initiatives at the U.S. Food and Drug Administration.

Pursue policies that advance cancer prevention, early detection, and control for individuals, families, and communities.

Support science-based policies that enhance and enforce tobacco prevention and control.

Ensure that recently enacted laws to advance progress against childhood cancers are fully implemented.



THE HONORABLE PATTY MURRAY
U.S. SENATOR FROM THE STATE OF WASHINGTON

" I will keep doing all I can to push back against policies that take us in the wrong direction, protect the progress we have made, and keep moving the ball forward, particularly when it comes to providing the investments needed to support the research we all know is so critical. "

November 1, 2017, AACR 110th Anniversary Celebration (by video greeting)

budget by $7 billion, a remarkable 23 percent increase. With this new trajectory of growth, the troubling trend of stagnant budgets that persisted for more than a decade has been halted. In addition, the NIH Innovation Fund, a multiyear, targeted funding stream created by the 21st Century Cures Act, is providing dedicated resources for the National Cancer Moonshot Initiative to further accelerate progress in priority areas where researchers are poised to make great strides in the next few years (see sidebar on **The National Cancer Moonshot Initiative**, p. 110).

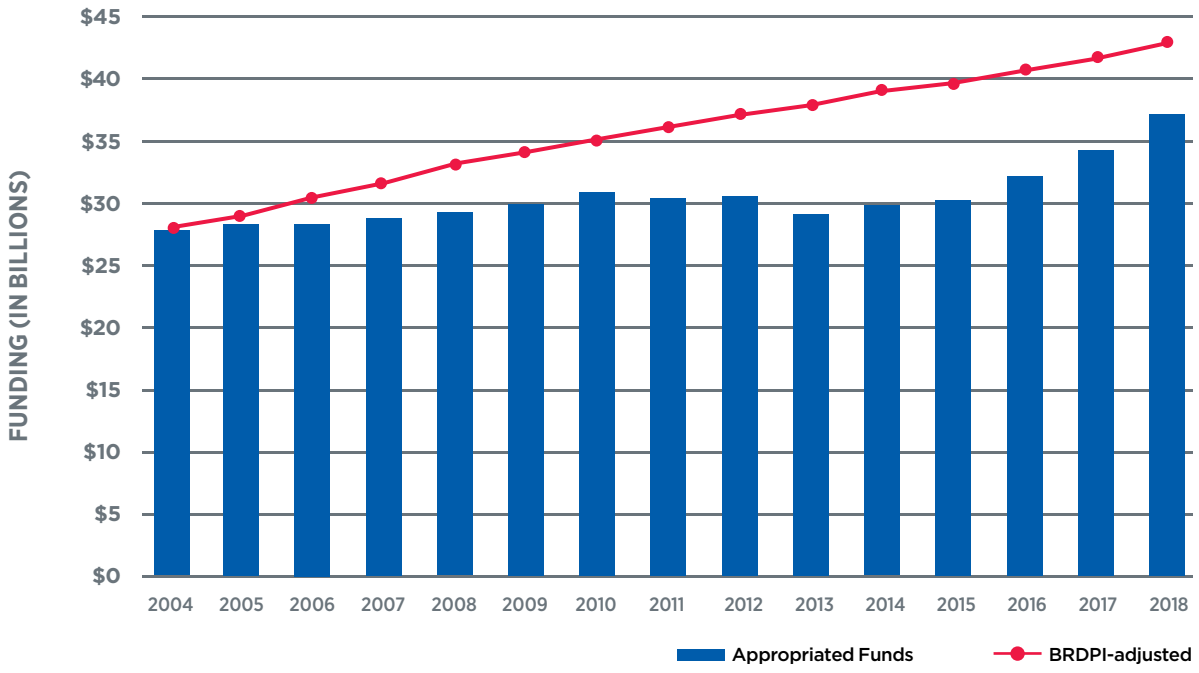
Funding for the NIH and NCI supports work across the spectrum of cancer research, from basic and population science to translational and clinical research, all of which are vital for making progress against cancer (see sidebar on **Biomedical Research: What Is It and Who Conducts It?** p. 52). Additionally, research on many cancers funded through the Department of Defense plays an important role and complements research projects funded by NIH (see sidebar on **Department of Defense Congressionally Directed Medical Research Programs**, p. 111).

As noted by **Congressman Ted Poe** (see p. 112), supporting biomedical research is one of the most important investments that our government can make, as it reaches all areas of the United States. In fact, more than 80 percent of the funds appropriated by Congress to the NIH are distributed to scientists in all 50 states, the District of Columbia, and around the world to conduct research. Now, thanks to funding increases in recent years, the NIH is awarding more than 60,000 research and training grants annually, 10,000 more than in 2015. The impact of federal support for the NIH and NCI reaches well beyond the laboratory and the clinic. As the largest single public funder of biomedical research in the world, NIH extramural funding generated $68.8 billion in economic activity last year alone.

Congress must stay the current course and prevent a return to an era of stagnant annual budgets at the NIH. A continued commitment from our elected leaders to robust annual increases for the NIH is imperative if we are to continue to spur progress and yield results for all Americans and people around the world.

FIGURE 19

NIH FUNDING: CLOSING THE GAP WITH THREE CONSECUTIVE YEARS OF ROBUST INCREASES



The biomedical research and development price index (BRDPI) reflects the rising cost of personnel, supplies, and equipment needed to conduct biomedical research. From 2004 to 2015, the National Institutes of Health (NIH) budget did not keep pace with BRDPI. Thanks to congressional leaders, the NIH has received three consecutive years of significant funding increases, which have resulted in the first real budget growth in more than a decade and a 23 percent increase in funding since fiscal year 2015.

A Strong, Diverse Research Workforce Depends on Predictable Funding

Many innovative research questions and fresh ideas come from scientists early in their careers. Ensuring the continued, rapid pace of progress against cancer requires that the next generation of cancer researchers be recruited, supported, and encouraged. A strong pipeline of talented researchers to whom current leaders in the field can pass the baton in the years to come will allow the work to continue in our efforts to conquer this disease.

The current generation of early-career investigators has been privy to the exciting advancements that have been described in this report. At the same time, they came of age in a decade when research funds were scarce, federal research budgets declined by more than 20 percent, and the path forward was uncertain. As we recommit to biomedical research as a national priority, our country must continue to invest in education and training of scientists at all career levels, but especially those who are in the early stages of their careers. The cancer workforce of tomorrow also must reflect the increasing diversity in our country, including disciplinary, gender, racial, ethnic, and geographic diversity. Robust, sustained, and predictable annual funding increases for the NIH, coupled with federal, state, and private sector-funded programs to assist early-career scientists, play an irreplaceable role in cultivating tomorrow's scientific leaders.

Members of Congress and NIH officials have recognized the importance of supporting scientists early in their careers, and they have taken steps to assist these investigators through legislative provisions in the 21st Century Cures Act and new policies enacted through the NIH Office of Extramural Research, including the Next Generation Research Initiative (see sidebar on **Fostering the Cancer Research Workforce of Tomorrow**, p. 114).

The NCI continues to identify ways to support early-career investigators. For example, in January 2018, the NCI announced the use of the Method to Extend

THE NATIONAL CANCER MOONSHOT INITIATIVE

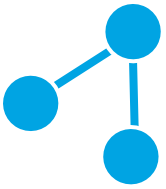
The National Cancer Moonshot Initiative seeks to accelerate cancer research to make more therapies available to patients while also improving our ability to prevent cancer and detect it at an early stage.

The 21st Century Cures Act, passed in 2016, authorized $1.8 billion over 7 years to fund the Cancer Moonshot. The same year, NCI convened a Blue Ribbon Panel (BRP) of many of the nation's top cancer experts – cancer researchers, oncologists, patient advocates, and private-sector leaders – to give careful thought to what could be done to expedite progress against cancer. To provide recommendations to the National Cancer Advisory Board, the BRP members collaborated with over 100 colleagues from across the cancer research community to identify 10 of the most compelling research opportunities poised for acceleration to help meet the goals of the Cancer Moonshot.

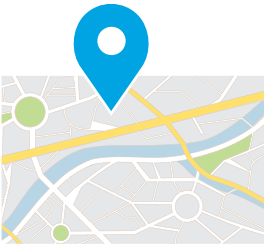
Implementation of the Moonshot is well under way, and over the past two fiscal years Congress has appropriated a total of $600 million for the Cancer Moonshot, which has enabled NCI to support and accelerate research in each of the 10 areas recommended by the BRP. In fiscal year 2017 NCI received its appropriation in May and was able to rapidly invest approximately $277 million in new research opportunities before the end of the fiscal year. NCI issued 17 new Cancer Moonshot funding opportunities in fiscal year 2018 and is in the process of finalizing awards.

The Cancer Moonshot is providing the research community with new resources to pursue critical research questions and to build upon collaborations to ensure their success. These opportunities for acceleration 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:

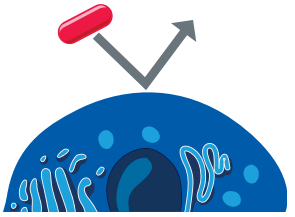
New adult and pediatric translational research immuno-oncology networks



Generation of a detailed 3-dimensional map of cancer to inform future cancer research

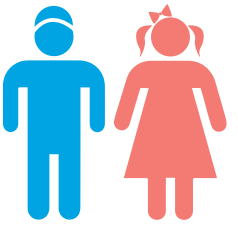


Innovative strategies to understand and combat tumor resistance to anticancer therapies

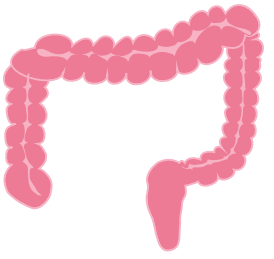


Improving the evidence-based follow-up care for individuals at high risk of cancer due to an inherited genetic susceptibility

Creation of a basic and translational research consortium to focus on unique drivers of childhood cancers



Accelerating colorectal cancer screening and follow-up through multilevel interventions



NCI is currently planning new research opportunities for FY 2019 and beyond. For more information and updates, visit: **cancer.gov/moonshot**

Research in Time (MERIT)(R37) Award to provide longer term grant support to early-career investigators. By providing an opportunity for longer term support for these individuals, the NCI hopes this will provide them with more opportunities to take creative risks and allow them to have additional time to successfully establish their careers before having to submit renewal applications. NCI Director Norman E. "Ned" Sharpless, MD, also announced at the AACR Annual Meeting in April 2018 that the NCI is increasing the number of R01s awarded to early-career investigators by 25 percent this year. The NCI's ability to take this step is a direct result of a greater federal investment in the NIH over the past three years.

POLICIES TO ADVANCE REGULATORY SCIENCE AT THE FDA

The FDA is an indispensable federal partner to the NCI in the quest to conquer cancer. It is imperative that the FDA receive consistent, robust support from Congress through annual appropriations because this funding supports regulatory science initiatives not funded through user fees. These initiatives seek to develop new evidence-based regulatory policies that promote cutting-edge innovation and expedited approval.

In recent years, Congress has recognized that it must equip the FDA with the resources it needs to support these regulatory processes. The 21st Century Cures Act included a supplemental, dedicated stream of funding, the FDA Innovation Fund, to assist the Agency over the next decade with increased responsibilities related to the Act. The law also expands hiring authority at the agency, and it ensures the continued professional development of staff.

In January 2017, the FDA established the Oncology Center of Excellence (OCE), which brings together regulatory scientists and reviewers with oncology expertise to expedite the evaluation of drugs, biologics, and devices for the treatment of cancer. Because of the coordinated clinical review made possible by its silo-busting intercenter structure, in its first year of existence, the OCE played a critical role in the approval of breakthrough therapies such as the first tissue-agnostic approval of a cancer treatment based on a biomarker (pembrolizumab) and the approval of two CAR T-cell therapies that harness the power of the patient's own immune system to fight cancer (tisagenlecleucel and axicabtagene ciloleucel). Within its first year of existence, the OCE approved 17 drug and biologic applications, 32 supplemental drug and biologic applications, and two biosimilar applications in oncology (252).

DEPARTMENT OF DEFENSE CONGRESSIONALLY DIRECTED MEDICAL RESEARCH PROGRAMS

Since 1992, Congress has appropriated funding for the Congressionally Directed Medical Research Programs (CDMRP) at the Department of Defense. The CDMRP funds groundbreaking research to transform health care for military service members and the American public. The CDMRP focuses on funding high-impact, high-risk and high-gain projects and is complementary to the work of other research agencies including the NIH. The CDMRP includes the following cancer research programs:

Program	Year Began	Total Funding (through FY 2017)	Projects Funded (through FY 2016)
Breast Cancer	FY 1992	$3.4 billion	6,728
Prostate Cancer	FY 1997	$1.62 billion	3,158
Ovarian Cancer	FY 1997	$296.5 million	401
Peer Reviewed Cancer*	FY 2009	$259.8 million	412
Lung Cancer	FY 2009	$113.5 million	195
Kidney Cancer	FY 2017	$10 million	N/A

*The Peer Reviewed Cancer Research Program (PRCRP) funds innovative basic, applied, and translational research with a focus on unique cancer risks faced by members of the Armed Services and their families due to environmental exposure. The PRCRP funds research related to many cancers, including bladder, colorectal, pancreatic, liver, and stomach cancers, melanoma, and lymphoma. For more information, see cdmrp.army.mil.

" **Money spent on research** is money well spent. "

© Karen Sayre

RAISING AWARENESS IN CONGRESS ABOUT THE VALUE OF BIOMEDICAL RESEARCH

Two years ago, my life, as I knew it, came to a screeching halt. All because of one word. Cancer. Since my diagnosis with leukemia, I have become much more aware of the impressive progress that we are making in the fight against cancer in the United States. Through my own cancer journey, I have also learned that our current efforts to fight this disease are not enough; we must do more. Many people are never really "cured" from cancer. The federal government has an important role to play in funding the research that will lead to new, more effective treatments and make our nation healthier.

My diagnosis with leukemia came in July 2016. I was participating in the Fourth of July parade in my hometown of Houston, Texas, when I realized how awful I felt. After the parade was over, one of my staffers tried to persuade me to go over to the local hospital. I was not having any of it. Instead, I boarded my flight and flew right back to Washington, D.C.—business as usual. However, when I arrived at the Capitol, I had to stop in the middle of the street I was trying to cross. I just couldn't make it all the way. Something was wrong. I turned around and went to Georgetown University Hospital.

The doctors at the hospital immediately began running test after test after test. Thinking I just had a bug, I returned to Capitol Hill and continued working. Later that day, the doctor called. I was to return to the hospital immediately. When I walked in, they sat me down and told me that they were diagnosing me with leukemia. I was shocked. I had no idea I was that sick.

I had heard of leukemia, but I only had a general understanding of the disease. But the doctors at Georgetown were amazing. They patiently explained my diagnosis and advised me to return home to Houston. After all, the University of Texas MD Anderson Cancer Center is one of the top cancer treatment facilities in the world. Before I could fly home, I had to have a platelet transfusion. I was in bad shape. The lifespan of platelets is very short, so I am very grateful to the three donors who came to the hospital that night and donated the platelets I needed. I'll never know their names or their faces, but they helped save my life that night.

The next morning, I boarded a plane to Houston and was immediately admitted to MD Anderson. After several long weeks as an inpatient, I was discharged and able to continue my treatment as an outpatient. The most important part of my cancer treatment is attitude and my faith in the Almighty. Staying positive is half the battle. In Congress, you have to be present to vote. So, we decided that I would continue my outpatient treatment at Georgetown University Hospital. I would continue serving the people of Texas as I received treatment. My treatment is still ongoing, but the leukemia is under control. I cannot thank the Good Lord and my doctors at MD Anderson and Georgetown University enough. The doctors who treat cancer patients are so well trained and passionate that I have full confidence that they will one day cure cancer.

During my treatment, I had the opportunity to speak to a lot of cancer patients. Cancer affects everyone, the very young, the very old, and everyone in between. Each of these individuals had a profound effect on me. The conversations taught me a lot about the successes and challenges of cancer treatment. What I learned, together with my own experiences, led me to work with Congressman Mark DeSaulnier to establish the bipartisan Congressional Cancer Survivors Caucus.

The Caucus's goal is to bring together members of Congress affected by cancer to discuss how we can work together for a future with even more individuals who wear the badge of survivor. One of the ways we can accelerate the pace of progress and make our society healthier is through adequate federal funding for research.

Money spent on research is money well spent. This is a message that I share with my colleagues in Congress. Most members are very open to hearing my message and learning how federal funding for research has made the fight against cancer possible. An increase in funding for the National Institutes of Health is pivotal to putting an end to cancer. Increasing awareness will ensure that Congress continues to make funding for research a priority.

And that's just the way it is.

FOSTERING THE CANCER RESEARCH WORKFORCE OF TOMORROW

The Next Generation Researchers Initiative (NGRI) aims to bolster support for early-stage and mid-career investigators by addressing the unique challenges they face as they begin and sustain independent research careers. Through the NGRI, the National Institutes of Health (NIH) is making additional funds available to do the following:

Extend the payline for early-stage investigators to 25 percent;

Extend the payline for mid-career investigators who are principal investigators and about to lose all NIH funding; and,

Identify "rising stars" who are seeking their second research project grant (RPG) but just missed the payline.

Included in the NIH FY 2019 budget request is a dedicated fund of $100 million for the NGRI in the Office of the Director to incentivize additional Institute and Center support for early-career investigators. The goal is to ramp up over several years to $1.1 billion annually across the NIH Institutes and Centers. The success of this initiative depends heavily on continued robust funding increases for NIH over the next several years.

Policy mandates established by the 21st Century Cures Act and other legislation accelerated efforts to characterize regulatory-grade real-world evidence and develop methodologies to support its regulatory use. Real-world evidence is clinical evidence regarding the usage and potential benefits or risks of a medical product derived from analysis of real-world data (see sidebar on **Real-world Evidence: Regulatory Practice and Promise**). Use of real-world evidence has broad potential applications to improve clinical care, accelerate research, and support regulatory decision-making.

To support these critical regulatory efforts and more, Congress provided the OCE with its first directed appropriation of $15 million into the Agency's base budget in FY 2018. There is broad support for providing the Center with $20 million in FY 2019.

In addition to the 21st Century Cures Act, another effort that gained significant momentum and resulted in the passage of new legislation in May 2018 by Congress is the concept of expanded access to experimental therapies, or "right-to-try" (see sidebar **Expanded Access and Right-to-Try**, p. 116).

THE HONORABLE LAMAR ALEXANDER
U.S. SENATOR FROM TENNESSEE

" When the Senate passed Cures, we hoped to unleash medical innovation and give Americans more access to life-changing treatments and cures, so more Americans could experience medical miracles. It is not an overstatement to say that the 21st Century Cures Act has the potential to affect virtually every American family by taking advantage of breathtaking advances in biomedical research. "

December 7, 2017, Senate HELP Committee hearing

POLICIES TO ADVANCE CANCER PREVENTION AND CONTROL FOR INDIVIDUALS AND COMMUNITIES

Public policies must support both scientific research and the application (or implementation) of that research through programs that benefit people, families, and communities (see sidebar on **CDC Cancer Prevention and Control Programs**, p. 116). Multiple factors, in addition to genes and biology, affect cancer mortality and quality of life. These factors include the environment in which people live and the impact of health behaviors, community support networks, and local, state, and federal policies and programs. Cancer prevention, detection, treatment, and survivorship programs are most effective when all these factors are considered. Scientific research can inform efforts to address these factors, so that we can reduce cancer rates, reduce cancer mortality, and improve the quality of life for cancer patients and survivors.

Among the most important factors in preventing and treating cancer is access to comprehensive health care coverage. The Affordable Care Act (ACA) (see sidebar on **Major Benefits Related to Cancer in the ACA**) continues to provide major benefits for all Americans, but especially

REAL-WORLD EVIDENCE: REGULATORY PRACTICE AND PROMISE

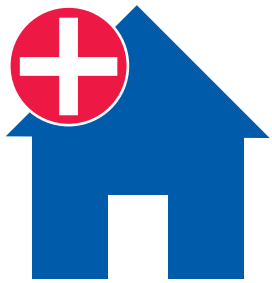
Real-world *data* are the data relating to patient health status and/or the delivery of health care routinely collected from a variety of sources. Real-world data can come from sources including:

electronic health records

product/disease registries

claims and billing

health-monitoring devices



patient-related activities in out-patient or in-home use settings

Real-world *evidence* is the clinical evidence regarding the usage and potential benefits or risks of a medical product derived from analysis of real-world data.

FDA has already been leveraging the power of real-world evidence for various purposes including regulatory decision-making, postmarket safety monitoring, and adverse event reporting.

The Center for Devices and Radiological Health (CDRH) regularly uses real-world evidence from sources including electronic health records and patient registries to support regulatory decision-making. CDRH reports over 50 regulatory decisions supported by real-world evidence.

The Sentinel Initiative, a decade-old endeavor to monitor the safety of medical products, relies on real-world data from electronic health records, disease registries, and insurance claims data.

CRDH's National Evaluation System for Health Technology is being built to more efficiently integrate real-world evidence into medical device decisions.

To build on these efforts to integrate real-world evidence into regulatory decisions, the FDA is going farther.

In 2017, the FDA released a guidance for industry, "Use of Real-world Evidence to Support Regulatory Decision-making for Medical Devices," to clarify for industry how real-world evidence is evaluated for medical devices based on their experience with previous reviews.

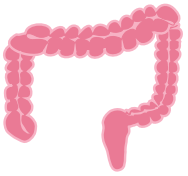
The Information Exchange and Data Transformation (INFORMED) program within the Oncology Center of Excellence seeks to expand organizational and technical infrastructure for big data analytics and examine modern approaches in evidence generation to support regulatory decisions.

CDC CANCER PREVENTION AND CONTROL PROGRAMS

The Centers for Disease Control and Prevention (CDC)'s Cancer Prevention and Control Programs are in every state and play an essential role in the prevention, detection, and treatment of cancer.

Since its inception in 1991, the National Breast and Cervical Cancer Early Detection Program has screened 12.7 million women and diagnosed 74,000 breast cancers and 4,000 cervical cancers, and has found more than 181,000 cervical lesions that if left alone would turn into cancer.

The Colorectal Cancer Control Program in its first year (2015) recruited 413 clinics serving more than 700,000 patients ages 50 to 75 years. Using proven strategies, the program screened 24,000 patients in those clinics—an average increase in screening of 5%.



The National Comprehensive Cancer Control Program (NCCCP) provides funding and technical advice to create, carry out, and evaluate comprehensive cancer control plans in all 50 states, the District of Columbia, 6 U.S. Associated Pacific Islands and Puerto Rico, and 8 tribes or tribal organizations. The NCCCP focuses on issues such as prevention, detection, treatment, survivorship, and health disparities.

State and territory cancer registries funded by the National Program of Cancer Registries (NPCR) collect and process more than 1.7 million new cancer cases annually. NPCR coordinates with NCI's SEER Program to collect cancer data on 100% of the U.S. population.

CDC also operates several critically important campaigns and initiatives aimed at educating the public and promoting cancer prevention and early detection, including:

- Prostate Cancer Awareness Campaign
- National Skin Cancer Prevention Education Program
- Ovarian Cancer Control Initiative
- Gynecological Cancer Education and Awareness (Johanna's Law)
- Cancer Survivorship Resource Center

For more information see cdc.gov/cancer.

EXPANDED ACCESS AND RIGHT-TO-TRY

Providing potentially lifesaving investigational drugs to terminally ill patients has long been a concern for patient and government groups, particularly when there are very few, if any, approved treatments for a particular disease. The U.S. Food and Drug Administration (FDA) has facilitated access to investigational drugs since the late 1980s. As a result of legislation, guidance, and collaborative projects, the Agency now authorizes greater than 99 percent of expanded access requests, usually within hours or a few days depending on the level of emergency. While the FDA approves almost every application it receives, the application process requires physicians to first request the use of an investigational therapy from that therapy's sponsor, and drug sponsors may choose not to provide a requested treatment.

Despite procedural improvements and the high rate of approvals under the FDA's expanded access process (sometimes known as "compassionate use"), right-to-try legislation was signed into law by President Trump on May 30, 2018. This law allows terminally ill patients who have exhausted FDA-approved treatment options and cannot participate in a clinical trial to request access to an experimental treatment from the sponsor, with their doctors' approval. Right-to-try legislation allows terminally ill patients to bypass the FDA in seeking experimental treatments, but as with expanded access, the sponsor may still approve or deny such applications.

In the wake of the bill's passage, the FDA is committed to ensuring patients remain protected. Since long before the law's passage, FDA Commissioner Scott Gottlieb and the Oncology Center of Excellence have been committed to finding the balance between ensuring patients are safe and approving effective, potentially lifesaving therapies as quickly as possible.

for cancer patients and survivors. Particularly valuable in terms of cancer prevention and control are provisions mandating coverage for preventive cancer screening and prohibiting denial of insurance coverage based on pre-existing conditions. Any modifications to existing health care coverage policy should maintain and strengthen these provisions to ensure all Americans share in the benefits of our national commitment to cancer prevention and control.

Elimination of HPV-related cancers is one area where advances in basic and clinical research, paired with results of population research, can be combined to spur policy that substantially reduces cancer mortality. In June 2018, the AACR joined all 70 NCI-designated cancer centers and five national cancer organizations in urging increased HPV vaccination and screening access to prevent the human devastation caused by HPV-related cancers. The organizations collectively recognized insufficient vaccination as a public health threat and called upon the nation's policy makers, physicians, parents, and young adults to take advantage of this unprecedented opportunity through vaccination to eliminate several different HPV-related cancers in men and women. Achieving the HPV-cancer elimination goal will require effective collaboration among a broad range of stakeholders, as well as policies and programs to strengthen HPV vaccination rates at the national, state, and local levels.

Growing differences in risk factor exposure and cancer outcomes between racial and ethnic groups, rural and urban populations, and insured/uninsured Americans highlight the need for health policy solutions that address disparities. Policy solutions that support coordination among federal agencies, state and local governments, and the communities they serve are important to reduce inequities in health care access, ensure high-quality care for all, and address social determinants of health. Improved engagement of minority communities as partners in research is one notable way in which NIH is working toward better understanding of disparities to help drive development of solutions.

The NIH All of Us program (a prospective study of one million Americans funded through the NIH Innovation Fund) is engaging communities across the country to ensure participants in this extensive research cohort reflect American diversity. Such diverse inclusion is intended to lay the groundwork for enabling men and women of all ages, races, and ethnicities to benefit from coming advances in precision medicine. In another example of NIH leadership on disparities, NCI is spearheading a rural cancer control initiative that funds population research and promotes national-level interagency collaboration to better understand rural disparities and test strategies for mitigating challenges rural communities face in cancer prevention and control.

TARGETING TOBACCO PRODUCTS THROUGH FDA REGULATION

Restricting the use of tobacco through regulatory policies has long had an important role in cancer prevention and improving outcomes for cancer patients (see sidebar on **Highlighting the New Corrective Advertisements**, p. 118). The AACR strongly believes that further progress can be made against cancer through the use of evidence-based strategies to prevent and control tobacco use (230) (253).

In July 2017, FDA Commissioner Scott Gottlieb, MD, announced that the agency's Center for Tobacco Products will focus their tobacco regulatory efforts on nicotine addiction. Although nicotine is not directly responsible for cancer-related deaths, it is a highly addictive compound, which makes it extremely difficult for users to quit using tobacco products. Through an Advanced Notice of Proposed Rulemaking (ANPRM), the FDA is beginning to look at lowering the nicotine content of combustible tobacco products and sought public input on the potential public health benefits and any possible adverse effects of lowering the nicotine content of combustible cigarettes. The FDA has issued additional ANPRMs on the role of

MAJOR BENEFITS RELATED TO CANCER IN THE ACA

The Affordable Care Act (ACA) provides major benefits that are especially important to preventing cancer and providing essential support for cancer patients and survivors. The ACA:

- Prohibits denial of insurance coverage based on pre-existing conditions;
- Enables access to cancer prevention and screening services;
- Allows young adults to remain covered under their parents' policies until the age of 26;
- Eliminates annual and lifetime coverage caps;
- Mandates ten "Essential Benefits" that have been vital for preventing and detecting cancer at earlier stages; and,
- Allows for Medicaid expansion at the state level.

menthol and kid-appealing flavors in tobacco products in attracting youth and on the definition and use patterns of premium cigars. The AACR, through its Science Policy and Government Affairs Committee, Tobacco and Cancer Subcommittee, publicly submitted ideas and suggestions on all of these particular requests for comments from the FDA.

In recent years, electronic nicotine delivery systems (ENDS) have become popular with adolescent and young adults. Some e-cigarette devices contain high levels of nicotine and have strong youth appeal as they come in a variety of flavors and are easily concealed through their resemblance to USB flash drives and a vapor cloud that dissipates quickly.

HIGHLIGHTING THE NEW CORRECTIVE ADVERTISEMENTS

More than 50 years after the U.S. Surgeon General first brought the relationship between cigarette smoking and lung cancer to the public's attention, tobacco companies are finally required to tell the truth about their deadly products. These "corrective ads" are designed to correct decades of misinformation that tobacco companies had spread about their products and highlight the following:

the adverse health effects of smoking;

lack of health benefit from smoking "low tar," "light," "ultra-light," "mild" and "natural" cigarettes (products that have been deceptively marketed as less harmful than regular cigarettes);

the addictiveness of smoking and nicotine;

manipulation of cigarette design and composition to ensure optimum nicotine delivery; and

adverse health effects of exposure to secondhand smoke.

Here's some history on how the corrective ads came to be.

1999 — U.S. Department of Justice sues major cigarette manufacturers Altria, Philip Morris USA, R.J. Reynolds Tobacco, and Lorillard, for violating civil provisions of the Racketeer Influenced and Corrupt Organizations Act (RICO), and other laws.

2006 — A U.S. District Judge finds the companies guilty of breaking civil racketeering laws by deceptively marketing to children and lying to the public about the dangers of smoking, and orders them to publish corrective statements on five topics about which they had deliberately deceived the public.

2006-2017 — For 11 years, tobacco companies filed numerous appeals trying to weaken the order and delay its implementation.

2017-2018 — Industry appeals were unsuccessful. Corrective ads began running in over 50 newspapers and on national prime-time television.

The tobacco companies must also publish the corrective statements on their websites and cigarette packs, although the implementation details of that are still being finalized.

To address these concerns, the FDA has:

- conducted a nationwide crackdown on the sale of e-cigarettes to minors at both brick-and-mortar and online retailers.
- contacted eBay to raise concerns over several listings for a specific, novel END product called JUUL, on its website. As a result, eBay swiftly removed the listings and voluntarily implemented new measures to prevent new listings from being posted to the web retailer's site.
- contacted e-cigarette manufacturers directly to request marketing information to understand and address why kids are finding these products appealing.
- issued, in conjunction with the Federal Trade Commission, warning letters to companies that misleadingly labeled or advertised nicotine-containing e-liquids as kid-friendly food products like juice boxes, candies, and cookies. E-liquids can be harmful, even deadly, to children.

POLICIES TO OVERCOME CHALLENGES IN PEDIATRIC CANCER

Cancer remains the second leading cause of death in children ages 1 to 14 (10). Over the past year, important strides have been made to further progress against pediatric cancers through the passage and implementation of two key pieces of legislation. In August 2017, Congress passed key provisions of the Research to Accelerate Cures and Equity (RACE) for Children Act of 2017. The RACE Act requires companies developing targeted cancer drugs for adults to develop those drugs for children with cancer as well. The law is a critical update to the Pediatric Research Equity Act (PREA) of 2003, which has led to important new safety and labeling information for other children's diseases but has had a minimal impact on childhood cancer due to several exemptions. Importantly, the RACE Act ends an exemption to PREA obligations for cancer drugs with orphan designations if the molecular target of the drug is relevant to a pediatric cancer. Since the passage of the RACE Act, the FDA has worked with NCI and other key opinion leaders to develop a list of pediatric-relevant molecular targets that will address regulatory uncertainty for industry and guide decision-making.

In May 2018, Congress passed the Childhood Cancer Survivorship, Treatment, Access, and Research (STAR) Act of 2018 (see sidebar on **The STAR Act Provisions**). This is the most comprehensive childhood cancer legislation passed by Congress to date, and it aims to address some of the most challenging issues in childhood cancer research and care.

THE STAR ACT PROVISIONS

The provisions of the Childhood Cancer Survivorship, Treatment, Access, and Research (STAR) Act do the following:

authorize the NCI to expand existing efforts to collect biospecimens for childhood cancer patients enrolled in NCI-sponsored clinical trials and to collect and maintain relevant clinical, biological, and demographic information on all children, adolescents, and young adults with cancer;

authorize grants to state cancer registries to identify and track incidences of child, adolescent, and young adult cancers;

authorize grants for pediatric cancer survivorship research and guide the Secretary of Health and Human Services to facilitate the identification of best practices for childhood and adolescent cancer survivorship care; and,

require that the National Cancer Advisory Board include at least one pediatric oncologist to ensure pediatric cancer research concerns are represented in recommendations to the NCI.

THE AACR CALL TO ACTION

Thanks to remarkable, bipartisan efforts in Congress, the NIH budget is back on a trajectory of real and sustainable annual growth following three consecutive years of robust funding increases that were significantly above the annual rate of biomedical inflation. Despite political and budgetary challenges, Congress has demonstrated an unwavering commitment to biomedical research by increasing the NIH budget by $7 billion, or 23 percent, since FY 2015. In addition to making medical research a national priority, both Congress and the administration have acknowledged the need for a strong FDA to ensure that research discoveries, once translated into therapies, are safe and effective, and reach the patients who need them as soon as possible.

We are at a pivotal moment in cancer research, and the positive funding momentum gained over the past three years must continue. During this time of both unprecedented scientific opportunity, and increasing incidence and associated mortality of cancer, the most valuable investments of federal dollars that Congress can make are in support of the medical research enterprise. This can most effectively be done through Congress providing robust, sustained, and predictable annual funding increases for the NIH. Annual increases in the NIH budget, coupled with consistent and sufficient funding for the FDA and the CDC in FY 2019 and beyond, will ensure the acceleration of the pace at which we make research discoveries and translate them into advances and population-based strategies that will save more lives from cancer.

We cannot continue to accelerate progress against cancer unless our elected leaders:

- **Continue to support robust, sustained, and predictable growth of the NIH budget** by providing an increase of at least $2 billion for NIH in FY 2019, for a total funding level of at least $39.1 billion.
- **Ensure that the $711 million in funding designated through the 21st Century Cures Act for targeted initiatives, including the National Cancer Moonshot, is fully appropriated in FY 2019 and is supplemental to the healthy increase for the NIH's base budget.**
- **Increase the FDA base budget in FY 2019 to $3.1 billion, a $308 million increase above its FY 2018 level,** to ensure support for regulatory science and to accelerate the pace of development of medical products that are safe and effective. Specifically, the AACR supports a funding level of $20 million for the FDA Oncology Center of Excellence in FY 2019.
- **Support the CDC Cancer Prevention and Control Programs with total funding of at least $517 million.** This includes funding for comprehensive cancer control, cancer registries, and screening and awareness programs for specific cancers.

By continuing to pursue an appropriations strategy that provides annual funding increases that are robust, sustained, and predictable for the NIH, NCI, FDA, and CDC, and by ensuring the funds available for the National Cancer Moonshot Initiative are fully appropriated in a way that supplements the NIH base budget, Congress can continue to help us transform cancer care, spur economic growth, and maintain our position as the global leader in science and medical research. Most importantly, it can help us save more lives from cancer.

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GLOSSARY

Acute lymphoblastic leukemia (ALL) An aggressive (fast-growing) type of leukemia (blood cancer) in which too many lymphoblasts (immature white blood cells) are found in the blood and bone marrow. Also called acute lymphocytic leukemia.

Acute myeloid leukemia (AML) A fast-growing cancer in which the bone marrow makes abnormal myeloblasts (a type of white blood cell), red blood cells, or platelets. It is also called acute myeloblastic leukemia, acute myelogenous leukemia, or acute nonlymphocytic leukemia.

Adjuvant therapy Additional cancer treatment that is given after the primary treatment is complete 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 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.

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. Also called molecular marker and signature molecule.

Biomedical inflation Biomedical inflation is calculated using the annual change in the Biomedical Research and Development Price Index (BRDPI), which indicates how much the NIH budget must change to maintain purchasing power. In general, the biomedical inflation rate outpaces the economy-wide inflation rate.

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 A term for cancers arising 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; see Human papillomavirus). Normal cells of the cervix do not suddenly become cancerous;

they first gradually develop precancerous changes, then later turn into cancer. These changes can be detected by the Papanicolaou (Pap) test and treated to prevent the development of cancer.

Chemotherapy The use of different 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 A group of cancers that start 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. Most 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.

Cyclin-dependent kinases (CDKs) A family of proteins that have important roles in controlling a number of cell processes, including cell multiplication. To function effectively, CDKs must attach to a small protein called a cyclin.

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.

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 mark on DNA (see Deoxyribonucleic acid) and histones (see Histone) 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.

Erdheim-Chester disease A rare multisystem disorder characterized by histiocytosis, a condition in which the immune system produces excess numbers of white blood cells called histiocytes. The histiocytosis leads to inflammation that can damage organs and tissues throughout the body; this tissue damage can lead to organ failure. Bone pain is the most frequent symptom of the disease.

Familial adenomatous polyposis (FAP) An inherited condition in which numerous polyps (see Polyp) can develop in the colon and rectum. It increases the risk of colorectal cancer. Also called familial polyposis.

Five-year survival rate The percentage of people in a specific group, for example, people diagnosed with a certain type of cancer or those who started a certain treatment, who are alive 5 years after they were diagnosed with or started treatment for a disease, such as cancer. The disease may or may not have come back.

GLOSSARY

Gastric cancer Cancer that arises in cells lining the stomach. Cancers starting in different sections of the stomach may cause different symptoms and often have different outcomes. Infection with the bacterium *Helicobacter pylori* is a major cause of gastric cancer, except for gastric cancers arising in the top portion of the stomach, called the cardia.

Gene The functional and physical unit of heredity passed from parent to offspring. Genes are pieces of DNA (see Deoxyribonucleic acid), and most genes contain the information for making a specific protein.

Head and neck cancer Cancer that arises in the head or neck region, including the nasal cavity, sinuses, lips, mouth, salivary glands, throat, or larynx (voice box).

Helicobacter pylori (H. pylori) A type of bacterium that causes inflammation and ulcers in the stomach or small intestine. People with H. pylori infections may be more likely to develop cancer in the stomach, including mucosa-associated lymphoid tissue (MALT) lymphoma.

Hepatitis B virus (HBV) A virus that causes hepatitis (inflammation of the liver). It is carried and passed to others through the blood and other body fluids. Different ways the virus is spread include sharing needles with an infected person and being stuck accidentally by a needle contaminated with the virus. Infants born to infected mothers may also become infected with the virus. Although many patients who are infected with HBV may not have symptoms, long-term infection may lead to cirrhosis (scarring of the liver) and liver cancer.

Hepatitis C virus (HCV) A virus that causes hepatitis (inflammation of the liver). It is carried and passed to others through the blood and other body fluids. Different ways the virus is spread include sharing needles with an infected person and being stuck accidentally by a needle contaminated with the virus. Infants born to infected mothers may also become infected with the virus. Although patients who are infected with HCV may not have symptoms, long-term infection may lead to cirrhosis (scarring of the liver) and liver cancer. These patients may also have an increased risk for certain types of non-Hodgkin lymphoma.

Hepatocellular carcinoma (HCC) HCC is the most common type of liver cancer that occurs mostly in people with chronic liver diseases, such as cirrhosis caused by hepatitis B or hepatitis C infection.

HER2 A protein found on the surface of some cells that can initiate a variety of signaling pathways, causing the cells to proliferate. It is found at abnormally high levels on the surface of many types of cancer cells, including some breast cancer cells, so these cells may divide excessively. Also called ERBB2 and NEU.

Histone A type of protein found in chromosomes. Histones attach to DNA and help control which genes are accessible for reading.

Hodgkin lymphoma A cancer of the immune system that starts in white blood cells called lymphocytes.

Hormone One of many chemicals made by glands in the body. Hormones circulate in the bloodstream and control the actions of certain cells or organs. Some hormones can also be made in the laboratory.

Human papillomavirus (HPV) A type of virus that can cause abnormal tissue growth (e.g., warts) and other changes to cells. Infection for a long time with certain types of HPV can cause cervical cancer. HPV also play a role in some other types of cancer, including anal, oropharyngeal, penile, vaginal, and vulvar cancers.

IDH1 and IDH2 Genes that make proteins called isocitrate dehydrogenase 1 and isocitrate dehydrogenase 2. These are enzymes that are used during the third step of the citric acid cycle to create molecules that are used for cellular energy.

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 incidence rate is defined as 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.

Liver cancer A cancer that forms in the tissues of the liver. The most common type of liver cancer is hepatocellular carcinoma.

Lymphatic vessels The thin tubes that carry lymph and white blood cells. Lymphatic vessels branch and grow, like blood vessels, by a process called lymphangiogenesis into all

the tissues of the body. Lymphatic vessels are an important part of the metastatic process.

Melanoma A form of cancer that begins in melanocytes (cells that make the pigment melanin). It may arise in a mole (skin melanoma), but it 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.

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.

Nanotechnology Science and technology conducted at the nanoscale, which is about 1 to 100 nanometers; for comparison, a sheet of paper is about 100,000 nanometers thick. Nanotechnology can be used in other fields of science, such as chemistry, biology, physics, materials science, and engineering.

National Cancer Institute (NCI) The largest of the 27 research-focused 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.

Neuroendocrine tumors Rare types of cancer that form from cells that release hormones into the blood in response to a signal from the nervous system. Neuroendocrine tumors can occur anywhere in the body, although most frequently they arise in the lungs, appendix, small intestine, rectum, and pancreas.

Non-Hodgkin lymphoma A term for a large group of cancers that arise in B cells or T cells. Non-Hodgkin lymphomas can be aggressive (fast-growing) or indolent (slow-growing) types. B-cell non-Hodgkin lymphomas include large B-cell lymphoma, follicular lymphoma, and mantle cell lymphoma. Cutaneous T-cell lymphoma is one example of a T-cell non-Hodgkin lymphoma.

Non–small cell lung cancer (NSCLC) A group of lung cancers that are named for the kinds of cells found in the cancer and how the cells look under a microscope. The three main types of NSCLC are squamous cell carcinoma, large cell carcinoma, and adenocarcinoma. NSCLC is the most common kind of lung cancer.

Oncology The branch of medicine that focuses on cancer diagnosis and treatment.

Phosphatidylinositol 3-kinases (PI3Ks) A family of proteins that work inside cells to send signals that direct numerous cellular functions, including cell growth, proliferation, and survival. The gene that encodes one component of one PI3K is mutated, resulting in an inappropriately active protein in many types of cancer, including some breast cancers.

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 each patient and her or his cancer. Also called personalized medicine, molecularly based medicine, individualized medicine, and tailored medicine.

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.

GLOSSARY

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 A form of cancer that starts in tissues of the prostate (a gland in the male reproductive system found below the bladder and in front of the rectum). In men, it is the most frequently diagnosed cancer and the second most common cause of death from cancer.

Prostate-specific antigen (PSA) A protein secreted by the prostate gland, increased levels of which are found in the blood of patients with cancer of the prostate.

Protein A molecule made up of amino acids that is needed for the body to function properly.

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.

Signaling pathway/signaling network A group of molecules in a cell that work together to control one or more cell functions, such as cell proliferation or cell death. After the first molecule in a pathway receives a signal, it alters the activity of another molecule. This process is repeated until the last molecule is activated and the cell function involved is carried out. Abnormal activation of signaling pathways can lead to cancer, and drugs are being developed to block these pathways. These drugs may help prevent cancer cell growth and kill cancer cells.

Standard of care The intervention or interventions generally provided for a certain type of patient, illness, or clinical circumstance. The intervention is typically supported by evidence and/or expert consensus as providing the best outcomes for the given circumstance.

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.

Thyroid cancer Cancer that arises in the thyroid gland (a gland at the base of the neck that makes hormones that help control heart rate, blood pressure, body temperature, and weight). The four main types of thyroid cancer—papillary, follicular, medullary, and anaplastic—are named for the kinds of cells found in the cancer and how the cancer cells look under a microscope.

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.

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.

* This list contains some of the specialized terms pertinent to the *AACR Cancer Progress Report 2018.*

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, 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 liopsome 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	trifluridine and tipiracil	Lonsurf
bladder cancer	valrubicin	Valstar

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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
multiple cancers	vinblastine	Velban
certain leukemias and lymphomas	vincristine	Oncovin
certain leukemias and lymphomas	vincristine sulfate liposomes	Marqibo
breast and lung cancers	vinorelbine tartrate	Navelbine

Antinutrients

Approved Indication	Generic Name	Trade Name
Certain leukemias	asparaginase	Elspar; Kidrolase

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

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.

* requires a companion diagnostic

SUPPLEMENTAL TABLE **2** *(CONTINUED)*

FDA-APPROVED THERAPEUTICS FOR THE TREATMENT OF CANCER

Radiation-emitting Drugs

Approved Indication	Generic Name	Trade Name
certain types of adrenal 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	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
multiple cancers	interferon alfa-2b	Intron A
melanoma; kidney cancer	aldesleukin	Proleukin
myelodysplastic syndrome; certain lymphomas	lenalidomide	Revlimid
multiple myeloma	pomalidomide	Pomalyst

Proteosome 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	Synribo mepesuccinate

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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 lymphomas	vorinostat	Zolinza

DNA Repair Inhibitors

Approved Indication	Generic Name	Trade Name
certain types of ovarian, fallopian tube, and primary peritoneal cancer	niraparib	Zejula
certain forms of breast and ovarian cancer	olaparib*	Lynparza
certain type of ovarian cancer	rucaparib*	Rubraca

Immune Checkpoint Inhibitors

Approved Indication	Generic Name	Trade Name
certain type of bladder cancer and lung cancer	atezolizumab	Tecentriq
certain types of bladder cancer and skin cancer	avelumab	Bavencio
certain types of bladder cancer and lung cancer	durvalumab	Imfinzi
melanoma	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	cabozantinib	Cometriq; Cabometyx
certain type of thyroid cancer; kidney cancer	lenvatinib	Lenvima
kidney cancer; soft tissue sarcomas; gastrointestinal stromal tumors	pazopanib	Votrient
certain types of lung and stomach cancers	ramucirumab	Cyramza
colorectal cancer, gastrointestinal stromal tumors, and liver cancer	regorafenib	Stivarga

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.

* requires a companion diagnostic

SUPPLEMENTAL TABLE **2** *(CONTINUED)*

FDA-APPROVED THERAPEUTICS FOR THE TREATMENT OF CANCER

Angiogenesis Inhibitors *(continued)*

Approved Indication	Generic Name	Trade Name
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
certain form of leukemia; certain form of lymphoma	obinutuzumab	Gazyva
certain leukemias	ofatumumab	Arzerra
certain lymphomas	rituximab	Rituxan

Oncolytic Virus

Approved Indication	Generic Name	Trade Name
melanoma	talimogene laherparepvec^	Imlygic

Therapeutic Vaccines

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

Cell-signaling Inhibitors

Approved Indication	Generic Name	Trade Name
certain type of breast cancer	abemaciclib	Verzenio
certain type of non-Hodgkin 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 leukemia	bosutinib	Bosulif
certain type of melanoma	binimetinib and encorafenib	Braftovi and Mektovi
certain type of lung cancer	brigatinib	Alunbrig
certain type of metastatic ALK-positive lung cancer	ceritinib	Zykadia
colon cancer*; head and neck cancer	cetuximab	Erbitux
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
some leukemias	dasatinib	Sprycel
some lung cancers*; pancreatic cancer	erlotinib	Tarceva
some pancreatic cancers; kidney cancer; non-cancerous kidney tumors; HER2+ breast cancers; neuroendocrine tumors	everolimus	Afinitor
lung cancer	gefitinib	Iressa
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
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
HER2+ breast cancer	pertuzumab	Perjeta
certain types of leukemia	ponatinib	Iclusig
certain type of breast cancer	ribociclib	Kisqali
myelofibrosis	ruxolitinib	Jakafi
most common type of skin cancer	sonidegib	Odomzo
multiple cancers	trametinib	Mekinist
HER2+ breast cancer	trastuzumab	Herceptin
kidney cancer	temsirolimus	Toricel; Torisel
thyroid cancer	vandetanib	Caprelsa
certain type of blood cancer and melanoma*	vemurafenib	Zelboraf
most common type of skin cancer	vismodegib	Erivedge

INCREASING PRECISION

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.

* requires a companion diagnostic

SUPPLEMENTAL TABLE **3**

SURGICAL AND RADIOTHERAPY TREATMENTS FOR CANCER

Type of Surgical Procedure	Description	Applicable cancer
Mastectomy	Surgery to remove part or all of the breast	Breast cancer
Lumpectomy	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 anad chest cancers
Laparoscopic surgery	Surgery done with the aid of a laparoscope	Variety of abdominal cancers
Reconstructive and limb-sparing surgeries	Surgery to restore the function or appearance of organs or tissues that were either removed or changed by cancer treatment; 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

Type of Radiation Procedure*	Description	Applicable cancer
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
Imaged 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

**ASTRO group 1 guideline

SUPPLEMENTAL TABLE **3**
(CONTINUED)

SURGICAL AND RADIOTHERAPY TREATMENTS FOR CANCER

Type of Radiation 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 surgery (adjuvant), sometime 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

INDEX

INDEX

O

P

Q

R

S

T

U

V

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