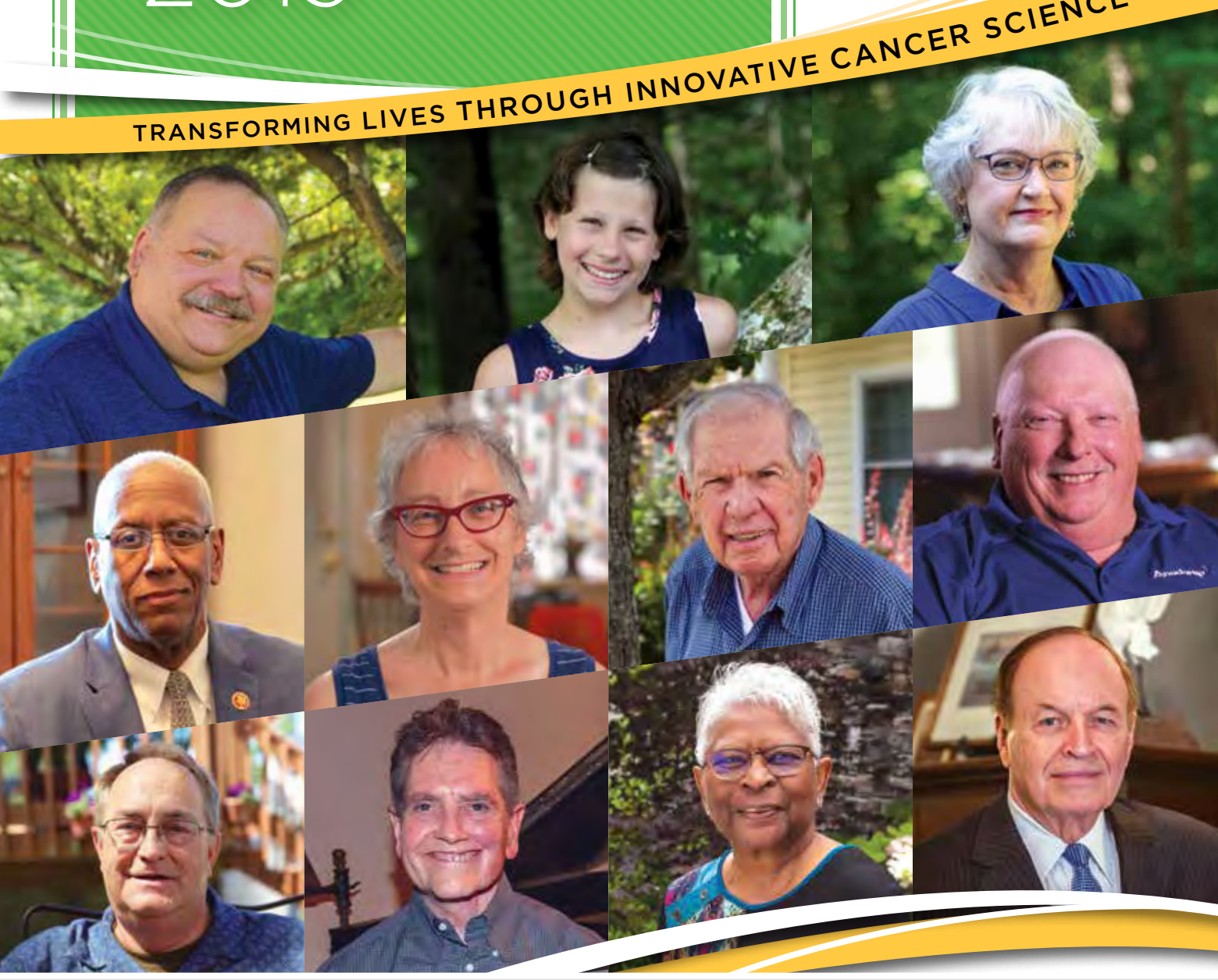
AACR CANCER PROGRESS REPORT 2019

AACR
American Association for Cancer Research®

FINDING CURES TOGETHER®

TRANSFORMING LIVES THROUGH INNOVATIVE CANCER SCIENCE



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ABOUT THE AMERICAN ASSOCIATION FOR CANCER RESEARCH

Founded in 1907, the American Association for Cancer Research (AACR) is the world's first and largest professional organization dedicated to advancing cancer research and its mission to prevent and cure cancer. AACR membership includes more than 42,000 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 www.AACR.org.

A MESSAGE FROM THE AACR

There has never been a greater time in history for the cancer field. In the United States, overall cancer incidence and death rates are declining, and the number of cancer survivors has reached a record high. This unparalleled progress against the collection of devastating diseases we call cancer is being driven by research that is spurring improvements in public health and breakthroughs across the spectrum of cancer care. Moreover, we are now poised to drive forward and deliver further transformative advances that will save more lives from cancer.

The AACR Cancer Progress Report 2019 provides a comprehensive overview of the remarkable progress we are making because of medical research, much of which is supported by federal investments in the National Institutes of Health (NIH). As highlighted in the report, federal funding for medical research has unleashed a surge in scientific discovery and technological innovation that has deepened our knowledge of the complexity of cancer and accelerated the rate at which this knowledge is being harnessed to develop new and better approaches to preventing, detecting, diagnosing, treating, and curing cancer.

In the past year, we have brought a record number of scientific advances to cancer patients in the form of new treatments for their diseases. Among the new treatments is the first molecularly targeted therapeutic approved for treating cancer based on the presence of a specific genetic biomarker in a patient's tumor, irrespective of the site at which the cancer originated. This milestone was made possible by decades of laboratory and clinical research. As we continue to unlock the secrets of the human genome, we will make more groundbreaking discoveries in cancer genomics and step further into the era of precision medicine, providing new hope for many more cancer patients who are awaiting more effective treatment options, including children, adolescents, and young adults with cancer.

The extraordinary expansion in the use of immunotherapy is continuing unabated, with new approvals for using this exciting approach to treatment for an additional three types of cancer, including a particularly intractable form of breast cancer called triple-negative breast cancer. The remarkable impact that immunotherapy has had on cancer care is highlighted by the fact that the researchers who conducted the landmark basic research that ignited the immunotherapy revolution were awarded the 2018 Nobel Prize in Physiology or Medicine for their seminal discoveries.

Even though more and more people are living longer, higher quality lives after a cancer diagnosis, we cannot escape the reality that there is a vital need for continued transformative research. This urgency is underscored by the sobering reality that cancer will claim more than 606,000 lives in the United States this year. This number is predicted to grow considerably in the coming decades largely because of overall population growth and because cancer is mainly a disease of aging, and the segment of the U.S. population age 65 and older is growing.

Moving forward, we need to ensure that there is no erosion of the spectacular progress we are making in curbing cigarette smoking, which is the leading cause of cancer in the United States. Thanks to the implementation of nationwide comprehensive tobacco control initiatives, the cigarette smoking rate among U.S. adults has fallen to 14 percent, down from 42 percent in 1965. This progress is at risk, however, because of the rapidly growing popularity of a new generation of tobacco products called electronic cigarettes (e-cigarettes).

E-cigarettes deliver very high levels of nicotine, which is extremely addictive, and emit numerous potentially toxic substances. Youth who use e-cigarettes are more likely to transition to conventional cigarettes. Therefore, the AACR is very concerned that the number of high-school and middle-school students using e-cigarettes jumped 78 percent and 49 percent from 2017 to 2018, respectively, and our organization is steadfastly committed to working with all stakeholders to address this emerging epidemic.

As we look to the future, we strongly believe that we have never been in a better position to maintain the positive momentum against cancer. The next wave of innovative breakthroughs that will transform cancer care is within our grasp. We have the scientific knowledge, cutting-edge technologies, and capability to deliver unprecedented advances to patients. We also have bipartisan leadership in Congress that has delivered four consecutive years of steady, significant annual funding increases for the NIH, which will help us take advantage of these extraordinary opportunities.

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

Elaine R. Mardis, PhD
AACR President

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

EXECUTIVE SUMMARY

There has never been a time of greater excitement in cancer science and medicine. The rapid pace and broad scope of the progress we are making against the collection of diseases we call cancer are astounding. This progress is happening because research discoveries made as a result of innovative cancer science are continually being translated to new and better approaches to cancer prevention, detection, diagnosis, treatment, and cure.

As the first and largest professional organization in the world dedicated to advancing every area of cancer research, the American Association for Cancer Research (AACR) is dedicated to increasing public understanding of cancer and the importance of cancer research for saving lives. It is also committed to advocating for increased annual federal funding to government entities that fuel progress against cancer and improve public health, in particular, the National Institutes of Health (NIH), National Cancer Institute (NCI), U.S. Food and Drug Administration (FDA), and Centers for Disease Control and Prevention (CDC).

The annual AACR Cancer Progress Report to Congress and the American public is a cornerstone of the AACR's educational and advocacy efforts. This ninth edition of the report highlights how research continues to extend and improve lives, like the lives of the courageous individuals featured in this report who have shared their experiences with cancer. It also underscores how unwavering, bipartisan support from Congress, in the form of robust and sustained annual increases in funding for the NIH, NCI, and FDA, is vital if we are to accelerate the pace of progress against cancer for the benefit of patients and their families everywhere.

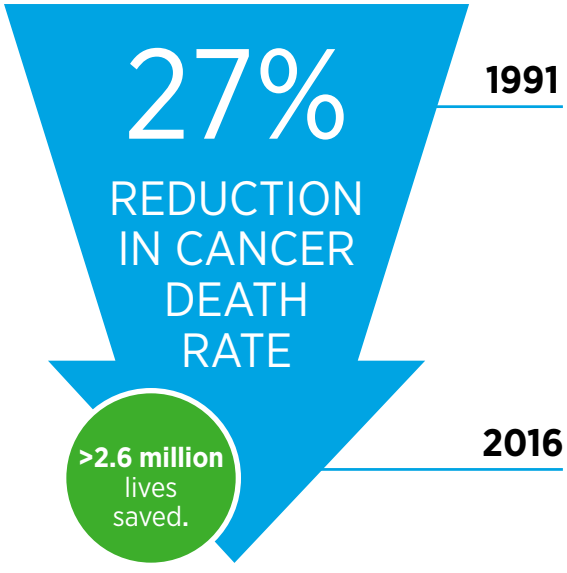
CANCER IN 2019

Research continues to be our best defense against cancer. It powers the development of new and better ways to prevent, detect, diagnose, treat, and cure some of the many diseases we call cancer. These advances are driving down overall U.S. cancer incidence and death rates, and increasing the number of children and adults who are living longer, higher-quality lives after receiving a cancer diagnosis. For example, the age-adjusted overall U.S. cancer death rate declined by 27 percent from 1991 to 2016, a reduction that translates into more than 2.6 million cancer deaths avoided. In addition, in the past 3 years, the number of adults and children living in the United States with a history of cancer rose by an estimated 1.4 million, reaching more than 16.9 million on January 1, 2019.

ELAINE R. MARDIS, PHD

AACR PRESIDENT, 2019–2020
Co-Executive Director, Institute for Genomic Medicine, Nationwide Children's Hospital, Columbus, Ohio

"Over the past 30 years, I have witnessed firsthand the coming of age of the field of cancer genomics research and its clinical applications."



Although we are making extraordinary advances every year, cancer is an enormous public health challenge. In fact, in the United States alone, it is predicted that 1.7 million new cases of cancer will be diagnosed in 2019 and that this number will rise, reaching more than 2.3 million in 2040. This sharp increase is anticipated largely because of overall population growth and because the segment of the U.S. population that accounts for most cancer diagnoses—those age 65 and older—is expanding. Another pressing challenge is ensuring that the U.S. health care system can withstand the burden of caring for the rapidly increasing numbers of cancer survivors because most of them have poorer health and quality of life than other individuals of a similar age.

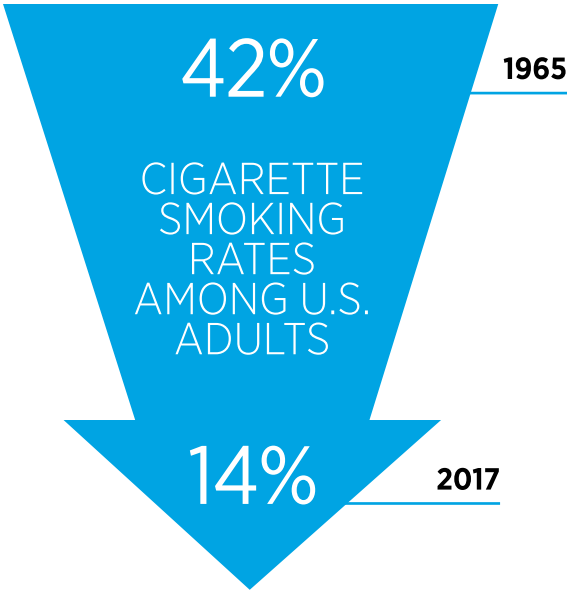
The immense toll of cancer is felt through both the number of lives it affects each year and its economic impact. In the United States, the direct medical costs of cancer care are estimated to have been $80.2 billion in 2015, the last year for which these data are currently available. This number does not include the indirect costs of lost productivity due to cancer-related morbidity and mortality, which are also extremely high. With the personal and economic burden of cancer predicted to rise in the next few decades, it is clear that the research that drives progress against cancer is a vital national investment.

UNDERSTANDING HOW CANCER DEVELOPS

Discoveries across the breadth of medical research have led to our current understanding of how cancer arises and develops.

We now understand that cancer is a collection of diseases that arise when the processes that control normal cell growth, division, and life span go awry. This happens primarily because of changes, or mutations, in the genetic material of normal cells. Individuals sometimes inherit a mutation, but most mutations are acquired over time. The identity of genetic mutations and the order and speed at which a cell acquires them determine the length of time it takes a given cancer to develop. Inherited cancer-causing mutations are linked to about 10 percent of cancer cases. Most mutations are acquired over an individual's lifetime due to errors arising during normal cell multiplication or because of exposure to external factors, such as toxicants in tobacco smoke and ultraviolet (UV) light from the sun.

Although genetic mutations underpin cancer initiation and development in most cases, epigenetic abnormalities as well as interactions between cancer cells and their environment—known as the tumor microenvironment—also play an important role. Ongoing research will continue to uncover additional cellular and molecular alterations that contribute to cancer development.



PREVENTING CANCER: IDENTIFYING RISK FACTORS

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

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

The development and implementation of public education and policy initiatives designed to eliminate or reduce exposure to preventable causes of cancer have reduced cancer morbidity and mortality in the United States. Thanks to such initiatives, cigarette smoking among U.S. adults has declined steadily over the past few decades, reaching the lowest rate ever recorded in 2017, 14 percent. However, the use of a new generation of tobacco products called electronic cigarettes (e-cigarettes) is rapidly increasing among U.S. youth and young adults. E-cigarettes deliver very high levels of nicotine, a highly addictive substance, and increase the risk of using combustible cigarettes among youth and young adults. The FDA and U.S. Surgeon General are taking steps to curb youth access to these tobacco products with new public education and policy initiatives, but more must be done to address this emerging epidemic.

The prevalence of obesity, another major risk factor, which is associated with 15 types of cancer, continues to rise among U.S. children and adults and according to recent estimates 35 percent of U.S. adults are physically inactive and only 25 percent of youth meet their recommended physical activity guidelines.

Therefore, it is imperative that all stakeholders work together to enhance the dissemination of our current knowledge of cancer prevention and implement evidence-based policies to minimize the incidence and death from preventable causes of cancer.

SCREENING FOR EARLY DETECTION

Research discoveries that have deepened our understanding of cancer initiation and progression are the foundation of screening strategies to detect precancerous lesions or cancer at an early stage of development. Finding precancerous lesions or cancer at an early stage of development makes it more likely that a cancer can be intercepted, and a patient treated successfully.

Cancer screening refers to checking for precancerous lesions or cancer in people who have no signs or symptoms of the cancer for which they are being checked. Determining whether broad implementation of a cancer screening test across 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. Currently, there are four types of cancer—breast, cervical, colorectal, and prostate cancer—for which screening tests have been used to screen large segments of the U.S. population who are at average risk of developing the cancer for which they are being screened.

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

TRANSFORMING LIVES THROUGH INNOVATIVE CANCER SCIENCE

The dedicated efforts of individuals working throughout the cycle of medical research are constantly powering the translation of new research discoveries into advances across the clinical cancer care continuum that are improving survival and quality of life for people in the United States and around the world.

Among the advances made from August 1, 2018 to July 31, 2019, are the 17 new therapeutics that were approved by the FDA for treating patients with various types of cancer. During the same period, the uses of 10 previously approved anticancer therapeutics were expanded by the FDA to include the treatment of additional types of cancer.

Two of these FDA approvals were groundbreaking advances.

In November 2018, the FDA approved the first molecularly targeted therapeutic for treating cancer based on whether a patient's tumor tests positive for a specific genetic biomarker, irrespective of the site at which the cancer originated. The therapeutic, larotrectinib (Vitrakvi), is providing a new treatment option and new hope to patients with a wide range of cancers, including children with soft tissue sarcoma, such as **Emma Levine** (see p. 68), and adults with salivary gland tumors, such as **Keith Taggart** (see p. 70).

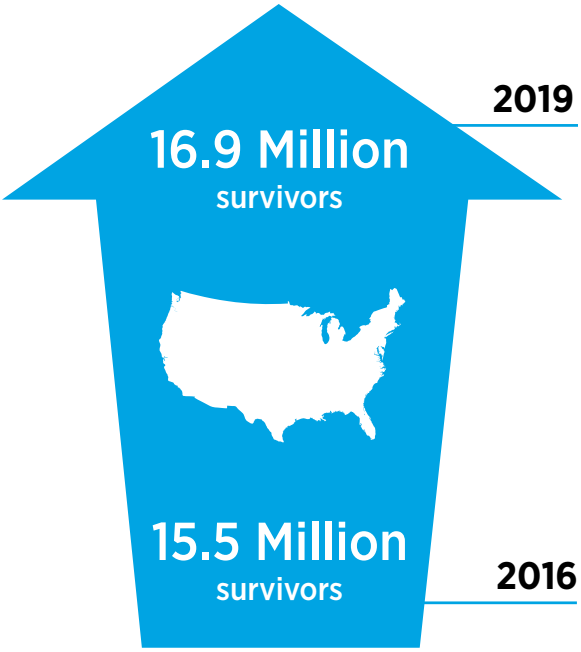
In March 2019, the FDA approved the first immunotherapeutic for use in the treatment of breast cancer. The immunotherapeutic, atezolizumab (Tecentriq), was approved for treating patients who are diagnosed with a particularly aggressive form of breast cancer called triple-negative breast cancer such as **Eva Joseph** (see p. 92).

SUPPORTING CANCER PATIENTS AND SURVIVORS

Research-fueled advances in cancer detection, diagnosis, and treatment are helping more and more people to survive longer and lead fuller lives after a cancer diagnosis. According to the latest estimates, more than 16.9 million U.S. adults and children with a history of cancer were alive on January 1, 2019, compared with just 3 million in 1971, and this number is projected to rise to 22.1 million by January 1, 2030.

Despite the progress, cancer survivors often face serious and persistent adverse outcomes, including physical, emotional, and psychosocial challenges because of their disease and treatment. Each person diagnosed with cancer faces a unique set of challenges, but one in four survivors reports a poor physical quality of life and one in 10 reports a poor mental health-related quality of life. Utilization of palliative care, adopting a healthy lifestyle, and participating in cancer prehabilitation and rehabilitation programs like the ones in which **Christine Cosby** took part (see p. 102) can improve quality of life.

The transition from initial cancer treatment to follow-up, long-term survivorship care can be complicated, and we



COMBATTING CANCER THROUGH SCIENCE-BASED, PATIENT-CENTERED POLICIES

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

If we are to continue to accelerate the pace of progress against cancer, we need robust, sustained, and predictable annual budget increases for the NIH and NCI. We also need continued congressional commitment to supporting the FDA and the cancer prevention and control programs at the CDC. These vital investments will help support a diverse research workforce, advance regulatory science initiatives, and allow us to pursue policies that improve cancer prevention, early detection, interception, and control for individuals, families, and communities.

need to identify the optimal way to provide comprehensive, coordinated care to all cancer survivors and ensure that it benefits patients by improving cancer-related outcomes and health-related quality of life. This will require a concerted effort from all stakeholders including patient advocates, such as **Tomma Hargraves** (see p. 96), whose experience with lung cancer led her to train to become a patient lay navigator so that she could help others diagnosed with the disease.

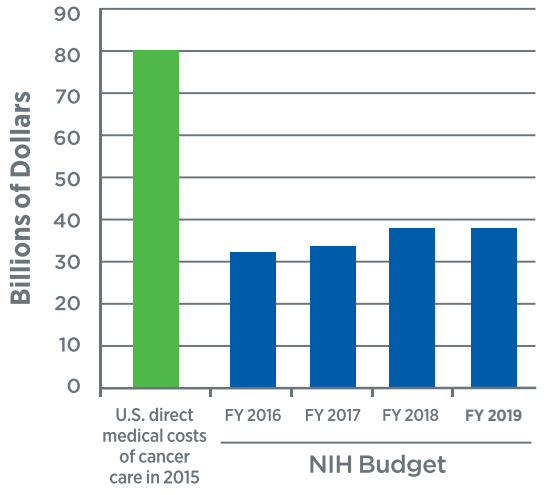
LOOKING TO THE FUTURE

Research is the backbone of progress because it provides us with a deep understanding of cancer.

As we look to the future, many researchers, including **AACR President Elaine R. Mardis, PhD,** (p. 106), 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, engineering, physical sciences, and computer science. The new wave of technological innovations driven by a team science approach will accelerate the pace of research discoveries across the breadth of cancer science and medicine. Cutting-edge techniques such as single cell sequencing and gene editing using CRISPR/Cas9 are poised to transform our basic understanding of cancer development, while the incorporation of novel technologies such as liquid biopsies and artificial intelligence into the clinic has the potential to transform patient care in the near future.

DIRECT COSTS OF CANCER CARE ARE STARTLING

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



THE AACR CALL TO ACTION

Research is driving progress against cancer because it is the foundation of every lifesaving clinical advance and every new policy designed to improve the health of the nation. These remarkable advances are illustrated by the declining cancer death rate and the rising number of children and adults who survive a cancer diagnosis.

Much of the research that is fueling these advances is supported by federal investments in the NIH. Strong, bipartisan support in Congress has resulted in four consecutive years of robust funding increases for the NIH. 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.

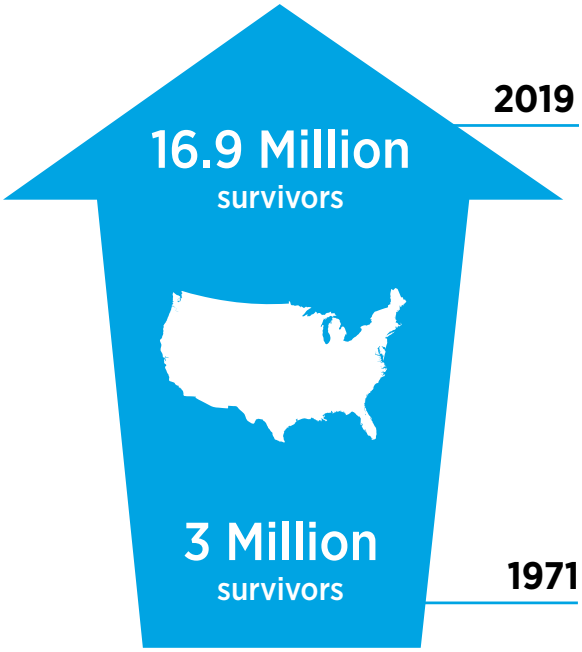
The enthusiasm and support for medical research are more than justified because we have unprecedented scientific knowledge and capability to deliver more advances across the continuum of cancer care in the future.

THAT IS WHY THE AACR URGES CONGRESS TO:

- Continue to support robust, sustained, and predictable growth of the NIH budget by providing an increase of at least $2.5 billion for NIH in fiscal year (FY) 2020, for a total funding level of at least $41.6 billion.
- Ensure that the funding designated through the 21st Century Cures Act for targeted initiatives, including the National Cancer Moonshot, is fully appropriated in FY 2020 and is supplemental to the increase in the NIH base budget.
- Support the FDA's critical regulatory science initiatives by providing an increase of at least $316 million in discretionary budget authority for medical products.
- Support the CDC Cancer Prevention and Control Programs with total funding of at least $555 million. This includes funding for comprehensive cancer control, cancer registries, and screening and awareness programs for specific cancers.

By providing robust, sustained, and predictable annual funding increases for the NIH, coupled with consistent and sufficient funding for the FDA and the CDC in FY 2020 and beyond, Congress will continue to help us transform cancer care, increase survivorship, spur economic growth, and maintain the United States' position as the global leader in science and medical research. These vital investments will not only strengthen the U.S. research enterprise, but also save more lives from cancer.

A SNAPSHOT OF A YEAR OF PROGRESS



BETWEEN AUGUST 1, 2018 AND JULY 31, 2019, THE FDA APPROVED:

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

10 **previously approved** anticancer therapeutics for treating new types of cancer

RESEARCH CONTINUES TO ADVANCE IMMUNOTHERAPY, LEADING TO:

The first therapeutic approved by the FDA for treating patients with advanced cutaneous squamous cell carcinoma, such as **Harold Sokoloff,** p. 88.

The first approval of a checkpoint inhibitor for treating patients with breast cancer, such as **Eva Joseph,** p. 92.

Four previously approved checkpoint inhibitors being approved for treating new types of cancer, including esophageal, kidney, liver, and lung cancers.

RESEARCH CONTINUES TO POWER PRECISION MEDICINE, LEADING TO:

The first therapeutic to target NTRK, which is providing new hope to patients with a wide array of cancer types, including children with soft tissue sarcoma, such as **Emma Levine,** p. 68, and adults with salivary gland tumors, such as **Keith Taggart,** p. 70.

The first CD22-targeted cytotoxin, which is allowing patients with hairy cell leukemia such as **Randy Surratt** to live in complete remission, p. 80.

The first therapeutic to target FGFR, which is benefiting patients with bladder cancer, such as **Gary Price,** p. 74.

CANCER IN 2019

IN THIS SECTION, YOU WILL LEARN:

- In the United States, the overall cancer death rate is decreasing, and the number of cancer survivors is increasing.
- In the past 3 years, the number of cancer survivors living in the United States increased by 1.4 million, reaching more than 16.9 million on January 1, 2019.
- Since the 1990s, the age-adjusted overall cancer death rate has decreased more rapidly among African Americans than among whites; however, the African American population still disproportionately shoulders the burden of overall cancer mortality.
- The economic burden of cancer is enormous, both in the United States and globally.

RESEARCH: DRIVING PROGRESS AGAINST CANCER

Research is the backbone of progress against cancer because it is the driving force behind every clinical advance that improves survival and quality of life, and every new policy designed to advance public health.

Every clinical advance and every policy that spurs progress against cancer is the culmination of a complex process that requires collaboration over the course of many years among numerous different stakeholders committed to fundamentally changing the face of this devastating disease (see sidebar on **Driving Progress against Cancer Together,** p. 9).

The remarkable progress being made against cancer—in particular, advances in reducing smoking rates, and in early detection, interception, and treatment of the disease—is causing cancer death rates to fall and the number of children and adults who survive a cancer diagnosis to rise (2). In fact, the age-adjusted overall U.S. cancer death rate declined by 27 percent from 1991 to 2016, a reduction that translates into more than 2.6 million cancer deaths avoided (2). In addition, in the past 3 years, the number of adults and children living in the United States with a history of cancer rose by an estimated 1.4 million, reaching more than 16.9 million on January 1, 2019 (3)(4).

Among the advances in cancer treatment that occurred during the 12 months covered by this report, August 1, 2018 to July 31, 2019, are the 17 new anticancer therapeutics approved by the U.S. Food and Drug Administration (FDA) for introduction into the clinic (see **Progress Across the Clinical Cancer Care Continuum,** p. 56). In addition, during this period, the uses of 10 previously approved anticancer therapeutics were expanded to include additional types of cancer.

CANCER: AN ONGOING PUBLIC HEALTH CHALLENGE

Although we have made incredible progress against cancer, it continues to be an enormous public health challenge in the United States and around the world (see sidebar on **Cancer: A Global Public Health Challenge,** p. 10) (2)(5). In the United States alone, it is predicted that 1,762,450 new cases of cancer will be diagnosed in 2019 and that 606,880 people will die from the disease (2) (see **Table 1,** p. 11).

VARIABLE PROGRESS AMONG TYPES OF CANCER AND STAGES OF DIAGNOSIS

Among the challenges we face is that progress against cancer has not been uniform for all types of cancer (8) or for all stages of a given type of cancer (8).

DRIVING PROGRESS AGAINST CANCER TOGETHER

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

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

policy makers;

health care providers;

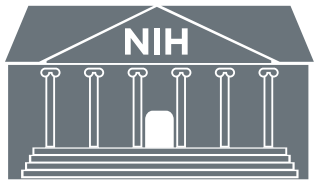
regulators;

academic and government researchers from a diverse array of specialties;

philanthropic organizations and cancer-focused foundations;

biotechnology, pharmaceutical, diagnostics, and medical device companies;

federal funding organizations; and



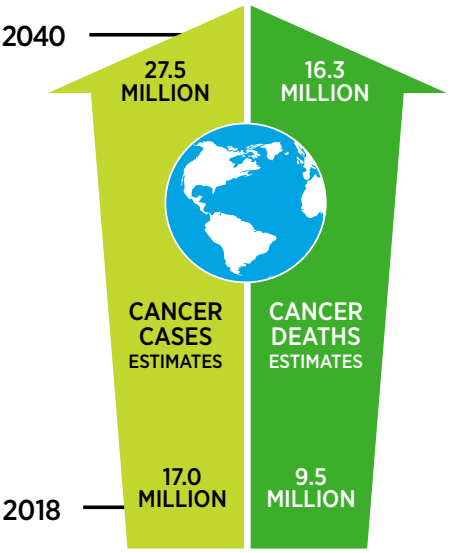
individual citizen advocates and members of advocacy groups;

payers.

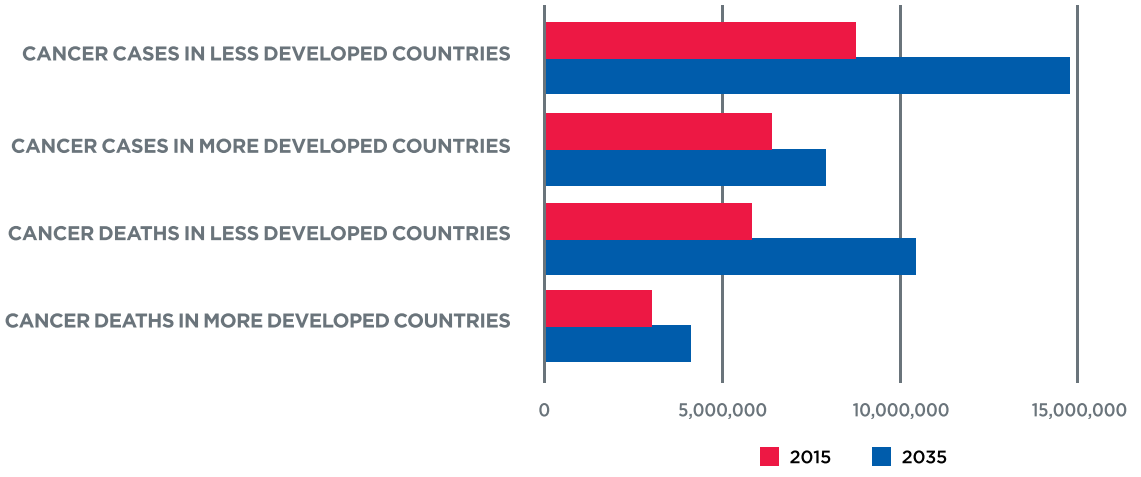
CANCER: A GLOBAL PUBLIC HEALTH CHALLENGE

The global public health challenge posed by cancer Is growing.

Cancer is a leading cause of morbidity and mortality around the world, accounting for about 16 percent of deaths worldwide (5). The devastating impact of cancer is predicted to grow significantly in the coming decades unless new and more effective approaches to cancer prevention, early detection, and treatment are developed and effectively implemented. The increase in the global burden of cancer will largely be fueled by overall population growth and expansion in the segment of the world's population most likely to develop cancer, those age 65 and older.



The increasing global burden of cancer is expected to be shouldered more by less developed regions of the world.



Given the growing global burden of cancer, it is imperative that the international 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 due to cancer, according to the International Agency for Research on Cancer (6).

Adapted from (7)

TABLE 1

ESTIMATED INCIDENCE AND MORTALITY FOR SELECTED CANCERS*

	ESTIMATED 2019 INCIDENCE			ESTIMATED 2019 DEATHS		
	TOTAL	MALE	FEMALE	TOTAL	MALE	FEMALE
All Sites	**1,762,450**	**870,970**	**891,480**	**606,880**	**321,670**	**285,210**
HEAD AND THORAX REGION						
Brain and other nervous system	23,820	13,410	10,410	17,760	9,910	7,850
Eye and orbit	3,360	1,860	1,500	370	200	170
Tongue	17,060	12,550	4,510	3,020	2,220	800
Mouth	14,310	8,430	5,880	2,740	1,800	940
Pharynx	17,870	14,450	3,420	3,450	2,660	790
Other oral cavity	3,760	2,710	1,050	1,650	1,290	360
Larynx	12,410	9,860	2,550	3,760	3,010	750
Lung and bronchus	228,150	116,440	111,710	142,670	76,650	66,020
Breast	271,270	2,670	268,600	42,260	500	41,760
GASTROINTESTINAL (GI) SYSTEM						
Esophagus	17,650	13,750	3,900	16,080	13,020	3,060
Stomach	27,510	17,230	10,280	11,140	6,800	4,340
Liver and intrahepatic bile duct	42,030	29,480	12,550	31,780	21,600	10,180
Gallbladder and other biliary	12,360	5,810	6,550	3,960	1,610	2,350
Pancreas	56,770	29,940	26,830	45,750	23,800	21,950
Small intestine	10,590	5,610	4,980	1,590	890	700
Colon and rectum	145,600	78,500	67,100	51,020	27,640	23,380
Anus, anal canal, and anorectum	8,300	2,770	5,530	1,280	520	760
UROGENITAL SYSTEM						
Kidney and renal pelvis	73,820	44,120	29,700	14,770	9,820	4,950
Ovary	22,530		22,530	13,980		13,980
Penis and other genital organs, male	2,080	2,080		410	410	
Prostate	174,650	174,650		31,620	31,620	
Testis	9,560	9,560		410	410	
Uterine cervix	13,170		13,170	4,250		4,250
Uterine corpus	61,880		61,880	12,160		12,160
Urinary bladder	80,470	61,700	18,770	17,670	12,870	4,800
Vulva	6,070		6,070	1,280		1,280
Vagina and other genital organs, female	5,350		5,350	1,430		1,430
SKIN (EXCLUDING BASAL & SQUAMOUS)						
Melanoma-skin	96,480	57,220	39,260	7,230	4,740	2,490
Other nonepithelial skin	7,870	5,100	2,770	4,420	3,290	1,130
HEMATOLOGICAL SYSTEM						
Acute lymphocytic leukemia	5,930	3,280	2,650	1,500	850	650
Chronic lymphocytic leukemia	20,720	12,880	7,840	3,930	2,220	1,710
Acute myeloid leukemia	21,450	11,650	9,800	10,920	6,290	4,630
Chronic myeloid leukemia	8,990	5,250	3,740	1,140	660	480
Other leukemia	4,690	2,860	1,830	5,350	3,130	2,220
Hodgkin lymphoma	8,110	4,570	3,540	1,000	590	410
Non-Hodgkin lymphoma	74,200	41,090	33,110	19,970	11,510	8,460
Myeloma	32,110	18,130	13,980	12,960	6,990	5,970
OTHER CANCERS						
Bones and joints	3,500	2,030	1,470	1,660	960	700
Soft tissue (including heart)	12,750	7,240	5,510	5,270	2,840	2,430

* Rounded to the nearest 10.

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

These challenges are illustrated by the fact that the 5-year relative survival rates for U.S. patients vary widely depending on both the type of cancer diagnosed and the stage at diagnosis (8). For example, the overall 5-year relative survival rates of 90 percent for women with breast cancer and 98 percent for men with prostate cancer stand in stark contrast to the overall 5-year relative survival rates of 18 percent for people with liver cancer and 19 percent for those with lung cancer. In addition, among women with breast cancer and people with colorectal cancer, those whose cancer is confined to the breast, or to the colon or rectum, have 5-year relative survival rates of 99 percent and 90 percent, respectively, while those whose cancer has metastasized have 5-year relative survival rates of 27 percent and 14 percent, respectively.

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

DISPARITIES IN PROGRESS FOR CERTAIN POPULATION GROUPS

Cancer health disparities are another pressing challenge.

The National Cancer Institute (NCI) defines cancer health disparities as adverse differences in cancer measures such as number of new cases, number of deaths, cancer-related health complications, survivorship and quality of life after cancer treatment, screening rates, and stage at diagnosis that exist among certain population groups (9) (see sidebars on **Which U.S. Population Groups Experience Cancer Health Disparities?** p. 13, and **U.S. Cancer Health Disparities,** p. 14).

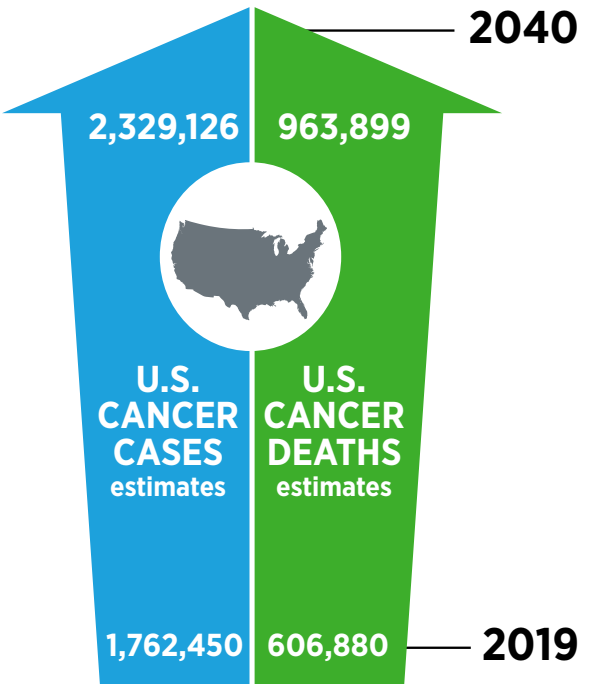
The African American population is one group that has long experienced cancer health disparities (14). For example, in 1990, the overall cancer death rates for African American men and women were 47 percent and 19 percent higher than they were for white men and women, respectively. In recent years, these disparities have narrowed to 19 percent and 13 percent higher for African American men and women, respectively, because overall cancer death rates have decreased more rapidly among African American men and women than they have among white men and women. However, the African American population still disproportionately shoulders the burden of overall cancer mortality compared with other racial/ethnic groups (10).

A significant proportion of the U.S. population is affected by cancer health disparities. Thus, it is important that we intensify research efforts designed to improve our understanding of the relative contributions of different factors that cause U.S. cancer health disparities (see sidebar on **Why Do U.S. Cancer Health Disparities Exist?** p. 15). Only with new insights obtained through research, including basic research using samples from all U.S. population groups, and through the participation of individuals from all these groups in clinical trials will we develop and implement interventions that will eliminate cancer for all.

THE GROWING POPULATION BURDEN OF CANCER

Unless we develop and effectively implement more effective strategies for cancer prevention, early detection, and treatment, the public health challenge posed by cancer will grow considerably in the United States and around the world in the coming decades (see sidebar on **Cancer: A Global Public Health Challenge,** p. 10) (2)(5).

In the United States, it is predicted that the number of new cancer cases and the number of cancer deaths will rise year after year, reaching more than 2.3 million and almost 1 million, respectively, in 2040 (16). These sharp increases over the current numbers are anticipated largely because of overall population growth and because the segment of the U.S. population that accounts for the majority of cancer diagnoses—those age 65 and older (8)—is expected to grow from 49 million in 2016 to 81 million in 2040 (2)(17). Also contributing to the projected increase in the number of U.S. cancer cases are the high rates of obesity among adults and children—which are nearly 40 percent and 20 percent, respectively—and the continued use of cigarettes by 14 percent of adults (18)(19).

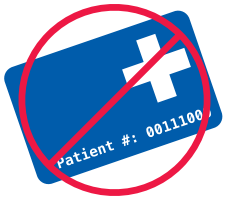


WHICH U.S. POPULATION GROUPS EXPERIENCE CANCER HEALTH DISPARITIES?

According to the National Cancer Institute, cancer health disparities in the United States are adverse differences in cancer measures such as number of new cases, number of deaths, cancer-related health complications, survivorship and quality of life after cancer treatment, screening rates, and stage at diagnosis that exist among certain population groups (9) including:

racial and ethnic minority groups;

individuals who lack or have limited health insurance coverage;



immigrants;

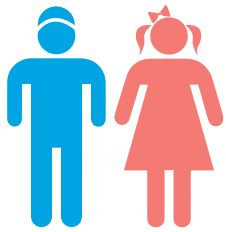
individuals with disabilities;

individuals of different ancestry

residents in certain geographic locations, including rural areas;

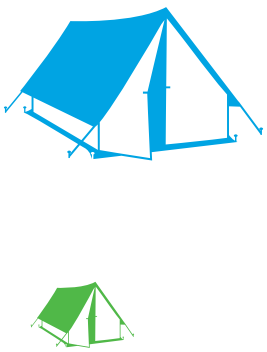
refugees or asylum seekers;

adolescents and young adults; and



individuals of low socioeconomic status;

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



the elderly.

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 **Which U.S. Population Groups Experience Cancer Health Disparities?** p. 13). Some recently identified examples of disparities in cancer incidence, mortality, and outcome are highlighted here. Disparities in other cancer measures are outlined elsewhere in the report (see sidebars on **Disparities in the Burden of Avoidable Cancer Risk Factors,** p. 26; **Disparities in Cancer Screening,** p. 49; **Disparities in Clinical Trial Participation,** p. 54; **Disparities in Cancer Treatment,** p. 64; and **Disparities in Health and Quality of Life after a Cancer Diagnosis,** p. 98).

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 (10).
2.6 TIMES MORE LIKELY	Hispanic children who have acute lymphocytic leukemia are **2.6 times more likely** to relapse than non-Hispanic children (11).
3.5 TIMES HIGHER	Men living in Kentucky have lung cancer incidence and death rates that are about **3.5 times higher** than those for men living in Utah (10).
HALF AS LONG	Patients with mantle cell lymphoma who have no health insurance have overall survival that is almost **half as long** as those with private health insurance (12).
35% HIGHER	Men living in the poorest counties in the United States have a colorectal cancer death rate that is **35 percent higher** than that for men living in the most affluent counties (10).
54% MORE LIKELY	Gay men are **54 percent more likely** to be diagnosed with cancer than heterosexual men (13).

Providing optimal care to the rapidly growing number of patients with cancer will require a substantially larger health care workforce than there is currently. For example, one recent study estimated that the number of patients worldwide requiring initial treatment with chemotherapy each year will increase from 9.8 million in 2018 to 15 million in 2040 and that the number of physicians required to optimally deliver this chemotherapy will rise from 65,000 to 100,000 (20).

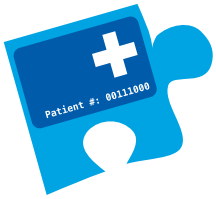
THE CHALLENGES ASSOCIATED WITH SURVIVORSHIP

The rapidly expanding population of cancer survivors, which encompasses all living people who have ever been diagnosed with cancer, is a testament to the significant progress we are making against the disease. However, this situation poses new challenges for all stakeholders committed to reducing the morbidity and mortality of cancer in the United States and around the world.

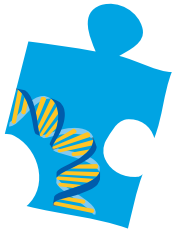
WHY DO CANCER HEALTH DISPARITIES EXIST?

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;

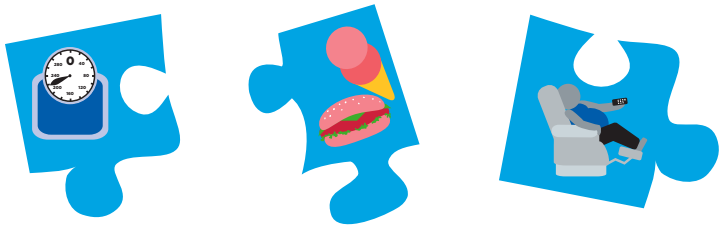
- cultural beliefs;

- exposure to environmental cancer risk factors;

- clinical trial participation;

- health literacy; and

- lifestyle, including weight, diet, and physical activity.



Adapted from (15)

One challenge posed by the growing population of cancer survivors is that most of these people have poorer health and quality of life than other individuals of a similar age (21). For example, one 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 (22). In 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.

As more and more people survive longer after a cancer diagnosis in the coming decades, the totality of their health care needs will grow significantly. Adding to the growing burden on the health care system is the fact that the proportion of cancer survivors who are age 65 or older is expected to increase from 64 percent in 2019 to 73 percent in 2040 and individuals in this age group tend to have more chronic health conditions than younger individuals (23).

Much work is needed to make sure that the health care system can withstand the impact of caring for the burgeoning population of cancer survivors (24). We also need to identify ways to improve quality of care and optimize quality of life for cancer survivors, as discussed in **Supporting Cancer Patients and Survivors** (see p. 94).

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 about $1.16 trillion in 2010 (25).

In the United States, the direct medical costs of cancer care are estimated to have been $80.2 billion in 2015, the last year for which these data are currently available (2). This number does not include the indirect costs of lost productivity due to cancer-related morbidity and mortality, which are also extremely high. In fact, one recent study estimated that cancer deaths among Americans ages 16–84 resulted in $94.4 billion in lost earnings in 2015 (26).

The cost of cancer care stands in stark contrast to the amount of money the federal government invests in medical research, most of which is administered through the 27 institutes and centers of the National Institutes of Health (NIH). The largest of these institutes and centers is the NCI, which is the federal government's principal agency for cancer research and training. In 2015, the same year that the direct medical costs of cancer care were $80.2 billion, the budget for the NIH 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, FY 2018, and FY 2019 have helped (see **Sustaining Momentum with Annual Funding Increases for Medical Research,** p. 111). To keep up with the pace of scientific innovation, it is imperative, however, that Congress continue to provide sustained, robust, and predictable increases in investments in the federal agencies that are vital for fueling progress against cancer, in particular the NIH, NCI, FDA, and Centers for Disease Control and Prevention (CDC), in the years ahead (see **The AACR Call to Action,** p. 124).

UNDERSTANDING HOW CANCER DEVELOPS

IN THIS SECTION, YOU WILL LEARN:

- Research provides our understanding of the biology of cancer, which is not one disease, but a collection of diseases characterized by the uncontrolled growth of cells.
- Genetic mutations underpin cancer initiation and development in most cases; the mutations are inherited in about 10 percent of cancer cases.
- Cancer initiation, development, and progression are strongly influenced by interactions among cancer cells and numerous factors in their environment.
- The more we know about the interplay among the individual factors influencing cancer in all populations, the more precisely and effectively we can prevent and treat cancer.

Over the past few decades, we have made tremendous progress in preventing, detecting, diagnosing, and treating cancer. This progress is epitomized by the declining overall cancer death rate and the rising number of cancer survivors (see **Research: Driving Progress against Cancer,** p. 8). It has been possible because of discoveries across the breadth of medical research, from basic science to translational and clinical research and population research, which have deepened our understanding of how cancer develops (see sidebar on **What Is Basic Research and How Does It Drive Progress against Cancer?** p. 18).

We now understand that cancer is a collection of diseases that arise when the processes that control normal cell growth, division, and life span go awry. As a result, cells start multiplying uncontrollably, fail to die, acquire blood vessels to obtain nutrients that support their altered cell biology, and begin to accumulate. In body organs and tissues, the accumulating cancer cells form masses called tumors, whereas in the blood or bone marrow they crowd out normal cells. Over time, some cancer cells may invade distant tissues, a process termed metastasis, by entering the bloodstream or lymphatic network, and form secondary tumors at remote sites.

CANCER DEVELOPMENT: INFLUENCES INSIDE THE CELL

The normal behavior of each cell in the human body is controlled by its genetic material, or genome. The genetic material comprises chains of deoxyribonucleic acid (DNA) units arranged in a certain order and packaged into condensed structures called chromosomes, which are contained within the cell's nucleus (see sidebar on **Genetic and Epigenetic Control of Cell Function,** p. 19). The order of the DNA units and how the DNA chains are packaged dictate which proteins and how much of them are made by each cell.

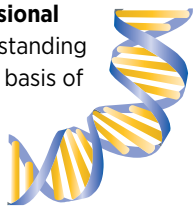
Alterations in the DNA sequence, referred to as mutations, can disrupt normal protein function and are the leading cause of cancer development (see sidebar on **Genetic Mutations,** p. 20). Each person's cancer has a unique combination of mutations, and as a cancer progresses, additional mutations accumulate. The number of cells within a growing tumor that carry a given mutation depends on when the mutation was acquired during tumor growth. Therefore, even within the same tumor, different cancer cells often have different combinations of genetic mutations. This variation, or heterogeneity, within a tumor or between a primary and metastatic tumor, is a leading cause of resistance to treatment.

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

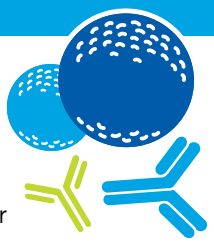
The National Institutes of Health (NIH) defines basic research as "the systematic study directed toward fuller knowledge or understanding of the fundamental aspects of a phenomenon and of observable facts without specific applications toward processes or products in mind." Basic research, however, has broad implications because it is fundamental to our understanding and treatment of human diseases, including cancer. The NIH spends more than half of its budget supporting basic research (27). NIH-funded basic research projects significantly contribute to novel target identification and drug development (28).

The following are selected examples of basic research discoveries that have transformed the field of cancer research:

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



Decades of basic research in **immunology** underpinned the development of immunotherapeutics that have revolutionized the field of cancer treatment (see **Figure 14,** p. 86).



Understanding the basic biology of **NTRK genes** and the discovery that NTRK gene fusions **fuel the growth of several types of cancer** laid the foundation for the development and FDA approval of the molecularly targeted therapeutic larotrectinib (Vitrakvi) (see **Figure 12,** p. 67).

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

Adapted from (7)

While inherited genetic mutations play a role in about 10 percent of all cancer cases (see **Table 2,** p. 21), most mutations are acquired over an individual's lifetime due to errors arising during normal cell multiplication or because of environmental exposures, lifestyle factors, or coexisting health conditions that fuel chronic inflammation (see sidebar on **Sources of Genetic Mutations,** p. 19). Scientists are actively investigating whether it is possible to identify the causative origins of a cancer by looking at the patterns of mutations in the cells that comprise it (29). Ongoing research is also uncovering the unique mutational landscapes of specific cancer types (30). For example, childhood cancers carry fewer single base changes, but more copy number variations and/or structural rearrangements, than cancers in adults (31)(32).

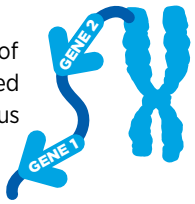
Not all mutations acquired by a cell lead to cancer. In fact, the genes that are mutated, and the order and speed at which a cell acquires mutations, determine whether a cancer will develop and, if a cancer does develop, the length of time it takes to happen. The progressive nature of cancer provides distinct time points for medical intervention to prevent cancer, detect and/or intercept it early, and treat progressive disease. In general, the further a cancer has progressed, the harder it 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. 40).

In addition to genetic mutations, changes in the physical structure of DNA caused by chemical modifications of the DNA and/or the proteins associated with it, termed

GENETIC AND EPIGENETIC CONTROL OF CELL FUNCTION

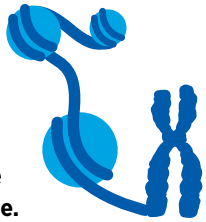
The genetic material of a cell comprises strings of four **deoxyribonucleic acid (DNA)** units called bases.

DNA bases are organized into **genes.** The order, or sequence, of the bases provides the code used 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 factors, called epigenetic marks, can tag DNA or attach to histones. The presence or absence of these factors determines whether a gene is accessible for reading. The sum of these marks across the entire genome is called the **epigenome.**



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

Adapted from (1)

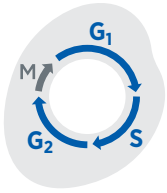
SOURCES OF GENETIC MUTATIONS

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

About 10 percent of all new U.S. cancer cases are linked to inherited or de novo genetic mutations, which are present in each cell of the body from birth (33)(34).

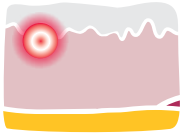
Most mutations, however, are acquired during a person's lifetime.

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



- Some occur because of persistent exposure to substances that damage genetic material, such as toxicants in tobacco smoke and ultraviolet radiation from the sun, (see **Figure 2,** p 25).

- Others occur as a result of chronic inflammation fueled by medical conditions such as Crohn's disease (35).



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

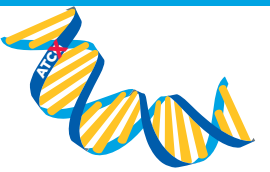
Adapted from (36)

GENETIC MUTATIONS

Types of genetic mutation known to lead to cancer include:

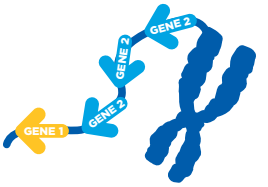
Single base changes

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



Extra copies of genes (gene amplification)

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

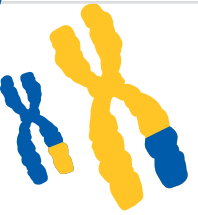


Deletions

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

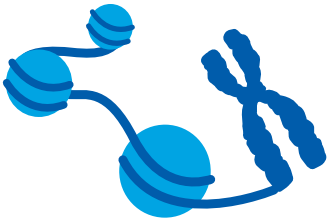
Structural variation

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



Mutations that alter the epigenome

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



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

Adapted from (1)

epigenetic modifications, can lead to cancer development (see sidebar on **Genetic and Epigenetic Control of Cell Function,** p. 19). Epigenetic modifications regulate how and when our genes are turned "on" or "off" and they are made by specialized proteins that "add" or "erase" unique chemical modifications on DNA and/or histones (37). In contrast to genetic mutations, epigenetic changes are often reversible, providing an opportunity for therapeutic intervention. Our understanding of the role of epigenetics in cancer is, however, still incomplete, and continued research is needed to fulfil the real potential of the epigenome in cancer science and medicine. For example, a recent report suggested that by looking at epigenetic patterns on DNA from blood, scientists may be able to predict which individuals are at a higher risk for cancer development (38).

Comprehensive analyses of human cancer genomes, such as those carried out through The Cancer Genome Atlas, have revealed numerous cancer-causing mutations. These discoveries have led to the development of a new class of molecularly targeted therapeutics that aim to rectify the cellular changes that arise due to cancer-causing mutations.

TABLE 2

INHERITED CANCER RISK

CANCERS	SYNDROME	ASSOCIATED GENE(S)
Leukemias and lymphomas	Ataxia telangiectasia	*ATM*
Basal cell carcinoma and medulloblastoma	Basal cell nevus syndrome	*PTCH1, PTCH2, SUFU*
All cancers	Bloom syndrome	*BLM*
Breast, ovarian, pancreatic, and prostate cancers	Breast-ovarian cancer syndrome	*BRCA1, BRCA2*
Breast, thyroid, and endometrial cancers	Cowden syndrome	*PTEN*
Breast and stomach cancers	Diffuse gastric and lobular breast cancer syndrome	*CDH1*
Colorectal 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 extrarenal 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, pleuropulmonary 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

While these advances have revolutionized cancer treatment, they have also brought attention to the fact that individuals of European ancestry are grossly overrepresented in most genomic investigations (39)(40). The lack of ethnic diversity in human genomic studies is limiting our understanding of cancer biology, including inherited cancer predisposition, in underrepresented populations. Rectifying this issue is an area of active research investigation.

CANCER DEVELOPMENT: INFLUENCES OUTSIDE THE CELL

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

The tumor microenvironment is a specialized niche surrounding the cancer cells in a tumor (see sidebar on **Cancer Growth: Local and Global Influences**). Bidirectional communications between cancer cells and their microenvironment affect tumor growth and metastasis (41)(42). Furthermore, the tumor microenvironment can shelter cancer cells from the effects of radiation, chemotherapy, and immunotherapy, thereby rendering them resistant to treatment (43). Future studies that uncover additional cellular and molecular properties of the tumor microenvironment will be vital for improving cancer diagnosis and treatment.

CANCER GROWTH: LOCAL AND GLOBAL INFLUENCES

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

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

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

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

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

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

Adapted from (44)

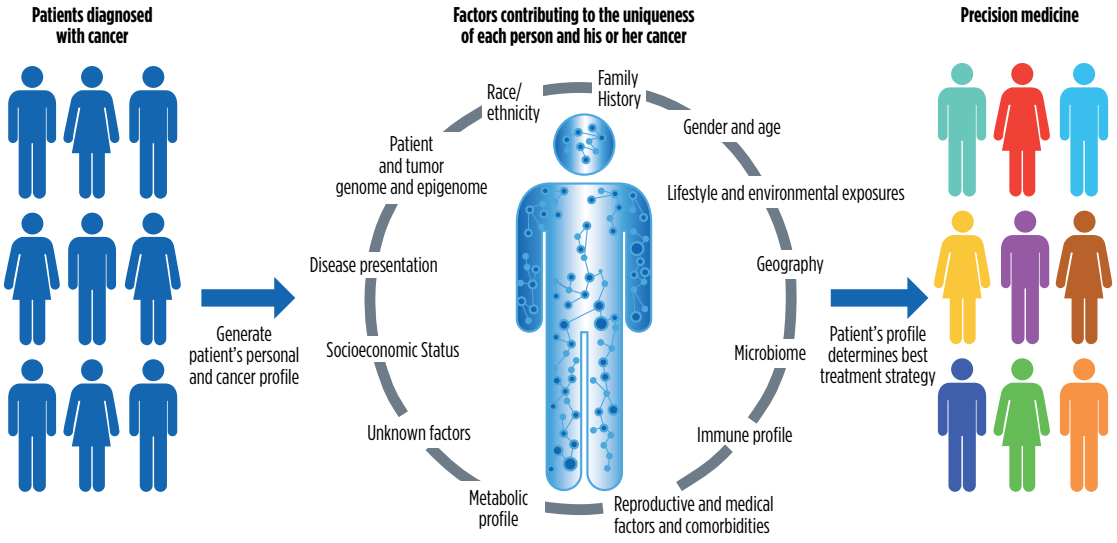
CANCER DEVELOPMENT: INTEGRATING OUR KNOWLEDGE

Over the past decade, we have made significant progress in how we understand and treat the complex group of diseases we call cancer. We have learned that each person's cancer is unique, in part because it is influenced by a patient's biological characteristics, environmental exposures, and lifestyle. As a result, we have seen a major shift from a "one size fits all" approach to cancer prevention, screening, and treatment to a more personalized approach called precision medicine. The aim of precision medicine is to use information about a person's genes, proteins, and environment to prevent, diagnose, and treat disease (see **Figure 1**).

Precision medicine aims to use genetic and other information about a patient's tumor, as well as other factors, to help diagnose, plan treatment, determine how well treatment is working, or make a prognosis, with the goal of improving clinical outcomes and minimizing unnecessary diagnostic and therapeutic interventions. Precision medicine approaches to treatment are already showing promise for certain patients with cancer (45). Nevertheless, our current knowledge of the underlying causes of cancer initiation and progression is still 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 from all stakeholders in the medical research community will be critical in order to realize the full potential of precision medicine.

FIGURE 1

PRECISION MEDICINE



Precision medicine is broadly defined as treating patients based on characteristics that distinguish them from other patients with the same disease. As shown in the figure, in oncology, the factors that contribute to the uniqueness of a patient and his or her cancer include, but are not limited to, the person's genome, the genome and epigenome of his or her cancer, disease presentation, gender, exposures, lifestyle, microbiome, and other comorbidities. Currently, genomics is the predominant factor influencing precision medicine, but as we learn more about the additional factors we can create an even more personalized approach to cancer treatment. It is important to note, however, that the cost-effectiveness of such profiling still needs to be evaluated alongside ongoing efforts that define which and to what extent such profiling improves outcomes for individuals.

Adapted from (15)

PREVENTING CANCER: IDENTIFYING RISK FACTORS

IN THIS SECTION, YOU WILL LEARN:

- In the United States, four out of 10 cancer cases and almost half of all cancer-related deaths are associated with preventable risk factors.
- Not using tobacco is the single best way 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 49 percent of U.S. adolescents have not received the recommended doses of the vaccine.

In the United States, the overall cancer death rate has been declining steadily over the past two decades, and the number of individuals living with a history of cancer has reached a record high. However, even in 2019, an estimated 606,880 people will die from cancer. Nearly half of these deaths will be attributable to cancers caused by potentially modifiable risk factors (46).

Thanks to decades of research, we have identified several factors that increase a person's risk of developing and/or dying from cancer, including cigarette smoking, excess body weight, unhealthy diet, exposure to ultraviolet (UV) radiation, and infection with certain pathogens (see **Figure 2,** p. 25). In fact, 40 percent of the cancer cases diagnosed in the United States in 2014 were caused by potentially modifiable risk factors (46). Given that several of these risk factors can be avoided, many cases of cancer could potentially be prevented. Many of the same risk factors are also associated with worse outcomes after a cancer diagnosis. Therefore, lifestyle modifications such as quitting smoking and increasing physical activity can improve health outcomes in cancer patients and survivors (see **Promoting Healthy Behaviors,** p. 100).

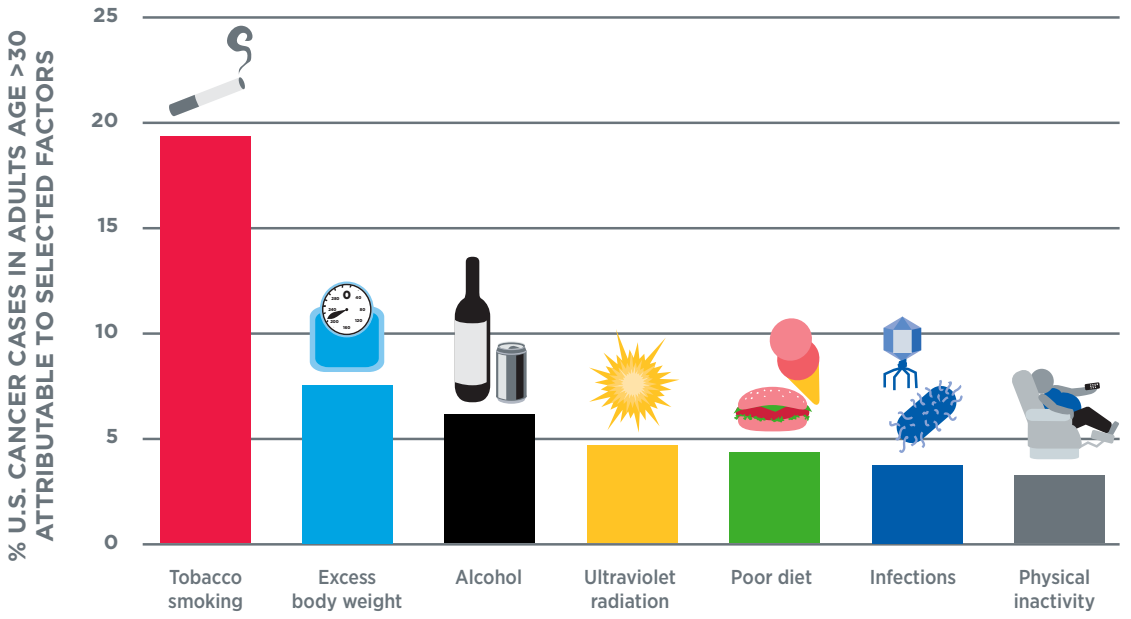
The development and implementation of public education and policy initiatives designed to eliminate or reduce

ECONOMIC IMPACT OF TOBACCO:

- Smoking-related illness in the United States costs more than $300 billion each year (57)(61).
- For cancer patients additional treatments that are attributed to continued smoking costs an extra $3.4 billion each year (62).
- FDA's "The Real Cost" campaign averted an estimated $31 billion in spending by preventing more than 175,000 youth from becoming established smokers (63).

FIGURE 2

INCREASING CANCER RISK



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

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

exposure to preventable causes of cancer have reduced cancer morbidity and mortality in the United States. For example, tobacco control efforts implemented since the 1960s have led to considerable reductions in smoking and smoking-related diseases, including lung cancer. Despite these measures, the prevalence of some of the major cancer risk factors continues to be high (47), particularly among segments of the U.S. population that experience cancer health disparities, such as racial and ethnic minorities, individuals from low socioeconomic backgrounds, and those with lower educational attainment (see sidebar on **Disparities in the Burden of Avoidable Cancer Risk Factors,** p. 26). Thus, we must identify more effective strategies for disseminating our current knowledge of cancer prevention and implement evidence-based interventions to reduce the burden of cancer for everyone.

ELIMINATE TOBACCO USE

Tobacco use is the leading preventable cause of cancer because it exposes individuals to many harmful chemicals that damage DNA, causing genetic and epigenetic alterations that lead to cancer development (53-55). Smoking tobacco has been shown to increase the risk of developing 17 different types of cancer in addition to lung cancer (see **Figure 3,** p. 27). Fortunately, quitting at any age can reduce these risks. In fact, the health benefits of cessation begin just weeks after quitting, and 10 years after quitting, the risks of all smoking-related cancers are reduced by 50 percent (56)(57). Thus, one of the most effective ways a person can lower his or her risk of developing cancer and other smoking-related conditions, such as cardiovascular, metabolic, and lung diseases, is to avoid or eliminate tobacco use.

DISPARITIES IN THE BURDEN OF AVOIDABLE CANCER RISK FACTORS

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

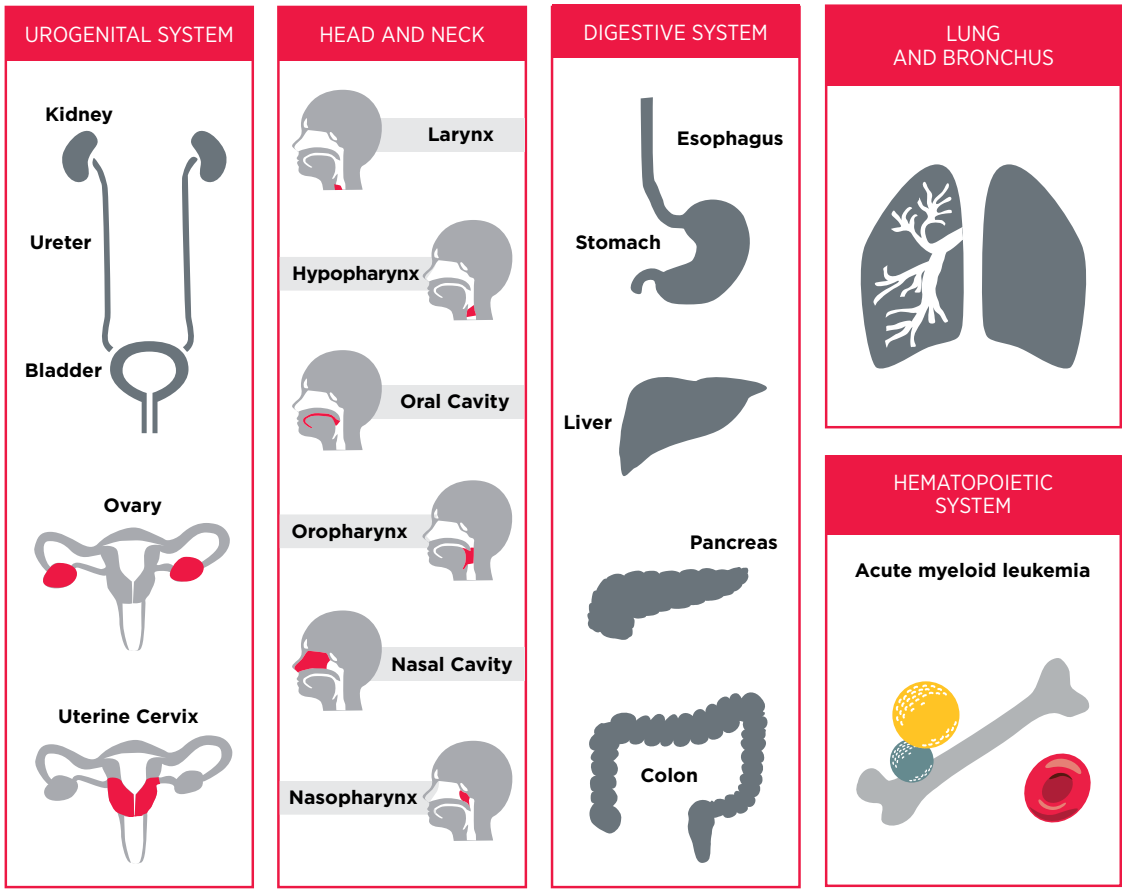
4 TIMES LESS LIKELY	College-educated individuals are nearly **4 times less likely** to smoke than those with a high-school education or less (47).
MORE THAN **TWICE**	The smoking rate among individuals who have serious psychological distress is **more than twice** that of those who do not (18).
40% HIGHER	Prevalence of adult tobacco use in Southern states, such as West Virginia, Kentucky, and Arkansas, is **more than twice** that in California; incidence of invasive lung, bronchial, and tracheal cancers is **40 percent higher** in the South than in the West (48).
55% VERSUS **38%**	Prevalence of obesity is higher among black women (55%) compared with white women (38%) (47).
21% VERSUS **39%**	Obesity prevalence among adults living in nonmetropolitan counties was 21% in Colorado compared to 39% in Louisiana (49).
28% VERSUS **15%**	American Indians/Alaska Natives have a higher prevalence (28%) of binge drinking compared with whites (24%) or Asian Americans (15%) (50).
6% VERSUS **45%**	Only 6% of non-Hispanic black and 24% of Hispanic fifth-graders reported using sunscreens compared with 45% of non-Hispanic whites (51).
56% VERSUS **41%**	Adolescents living in metropolitan areas are more likely to be up to date with human papillomavirus (HPV) vaccination (56%) compared with those in nonmetropolitan areas (41%) (52).

Thanks to the implementation of nationwide comprehensive tobacco control initiatives, cigarette smoking among U.S. adults has been declining steadily and reached an all-time low of 14 percent in 2017—a 67 percent reduction since 1965 (18). Exposure to secondhand smoke, which increases the risk of lung cancer among nonsmokers, has also dropped substantially over the past three decades (58). Consequently, the incidence of tobacco-associated cancers has been declining, and a recent report projects that the number of annual lung cancer deaths will drop by 63 percent within the next 50 years if the smoking rate continues to decrease in the future (48)(59).

Despite these positive trends we cannot overlook the fact that 34 million adults were still smoking cigarettes in 2017 (18). There are also striking sociodemographic disparities in

FIGURE 3

BEYOND THE LUNGS: CANCERS CAUSED BY SMOKING TOBACCO



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

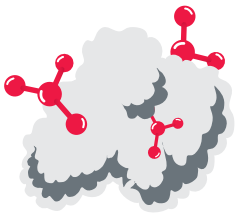
Figure adapted from (1)

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 identify evidence-based population-level interventions such as tobacco price increases, public health campaigns, age and marketing restrictions, cessation counseling and medications, and smoke-free laws to reduce smoking rates and smoking-related cancer burden in the United States. For instance, based on evidence that nearly 95 percent of adults who smoke report trying their first cigarette before the age of 21, 17 U.S. states have passed legislation to raise the minimum legal sale age for tobacco products to 21. This is a critically important strategy to reduce the burden of tobacco use because a recent report estimated that raising the minimum age for purchase of all tobacco products to 21, nationwide, could prevent 223,000 deaths among people born between 2000 and 2019, including 50,000 fewer deaths from lung cancer (60).

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

Electronic cigarettes (e-cigarettes) are battery-powered devices that provide nicotine, flavorings, and other additives to the user in the form of an aerosol (66). By December 2017, JUUL held the largest market share of any e-cigarette in the U.S. (67).

Constituents



- In addition to nicotine, they contain and emit numerous potentially toxic substances including heavy metals, volatile organic compounds, tobacco-specific nitrosamines, aldehydes, phenolic compounds, and polycyclic aromatic hydrocarbons
- One JUUL pod delivers as much nicotine as a pack of cigarettes; exposure to other toxic substances is lower

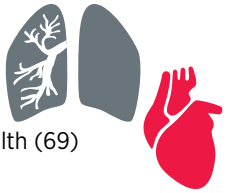
Use

- Highest among youth and young adults
- Use among high-school students: 1.5% in 2011 to 21% in 2018 (68)

Role in smoking cessation and initiation

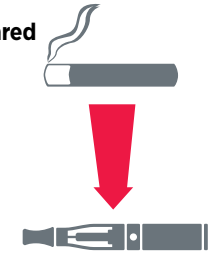
- More research is needed to evaluate their value as smoking cessation aids
- Increases the probability of youth transitioning to conventional cigarettes

Human health effects



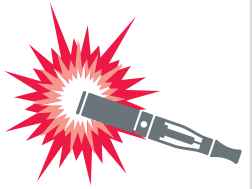
- There are early indications that vaping can pose significant risks to heart health (69)
- There is an urgent need for additional research to evaluate long-term health risks, including cancer, cardiovascular and pulmonary diseases, and pregnancy outcome

Possible harm reduction compared to combustible tobacco



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

Poisoning, injuries, and other health hazards



- Intentional or accidental exposure to e-liquid (from drinking or other contact) can have serious adverse health effects
- E-cigarettes can explode causing burns and other injuries
- The FDA and CDC are aware of and investigating the causes of numerous cases of seizures and severe lung illnesses following e-cigarette use, mostly in youth and young adults (70)

FDA, U.S. Food and Drug Administration; CDC, Centers for Disease Control and Prevention. Adapted from (7)

The use of other combustible tobacco products (for example, cigars), smokeless tobacco products (for example, chewing tobacco and snuff), and waterpipes (hookahs) is also associated with adverse health outcomes including cancer (64). Electronic cigarettes (e-cigarettes) are a rapidly emerging tobacco product. An alarming trend in recent years has been the growing popularity of e-cigarettes among U.S. youth and young adults. E-cigarettes were first introduced to the U.S. market in 2007 and since 2014 have been the most commonly used tobacco product among U.S. middle- and high-school students (65) (see sidebar on **E-Cigarettes: What Have We Learned and What Do We Need to Know?**).

The recent surge in e-cigarette use among youth coincides with the growing popularity of JUUL, a brand of e-cigarettes

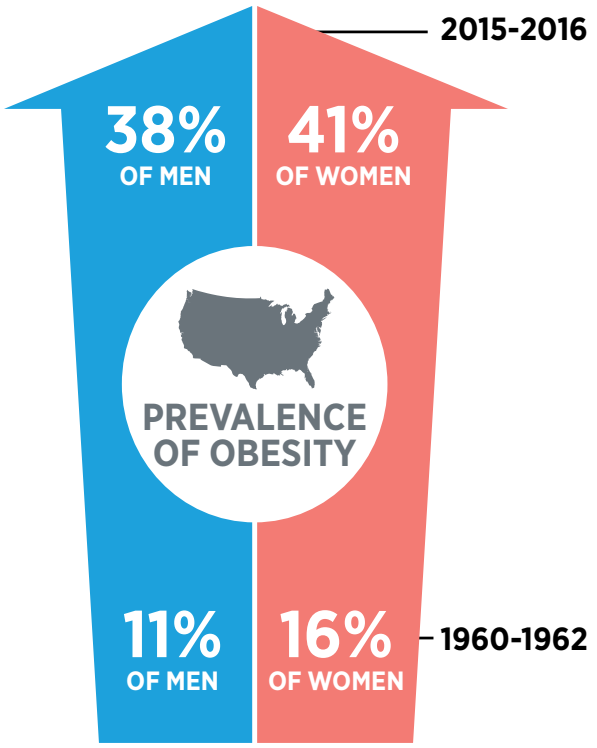
that are shaped like USB flash drives and can be used discreetly in schools or public settings (67). These products come in flavors that appeal to youth and deliver very high levels of nicotine, an extremely addictive substance that is harmful to the developing brain (71). According to recent studies, many users are unfortunately unaware that they are exposed to the same amount of nicotine as tobacco smokers (72)(73). There is also evidence that the use of e-cigarettes may act as a gateway to smoking combustible cigarettes by youth (66)(74). Thus, it is very concerning that the current use of e-cigarettes increased by nearly 80 percent and 50 percent among high-school and middle-school students, respectively, between 2017 and 2018 (68). Evidently, current policies to limit the spread of e-cigarettes among youth have been inadequate.

In the past year, the FDA has proposed several restrictions on e-cigarettes to curb youth access, and in December 2018, the Office of the U.S. Surgeon General issued an advisory declaring e-cigarette use in youth an epidemic (see **Supporting Public Health Policies to Reduce the Use of Tobacco Products,** p. 121). It is imperative that all stakeholders continue to work together to determine the long-term health outcomes associated with e-cigarettes and identify new strategies to implement population-level regulations to reduce e-cigarette use among youth and young adults.

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

About 20 percent of new cancer cases and 16 percent of cancer deaths in U.S. adults are attributable to a combination of being overweight or obese, poor diet, physical inactivity, and excessive alcohol consumption (46). Being overweight or obese as an adult increases a person's risk for 15 types of cancer. Conversely, being physically active reduces risk for eight types of cancer (see **Figure 4,** p. 30). 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 by Maintaining a Healthy Weight, Being Physically Active, and Consuming a Balanced Diet,** p. 31). Identifying the ways in which obesity, unhealthy diet, and physical inactivity increase cancer risk is an area of active research investigation.

The prevalence of obesity has been rising steadily in the United States and around the globe. According to the latest estimates, nearly 40 percent of adults in the United States are obese (47) while nearly 5 and 10 percent of all cancer cases in men and women, age 30 or older, can be attributed to excess body weight (19). Globally, excess body weight is responsible for about 4 percent of all cancer cases (75). Beyond cancer, obesity increases the risk of developing several other health



Data from (47)

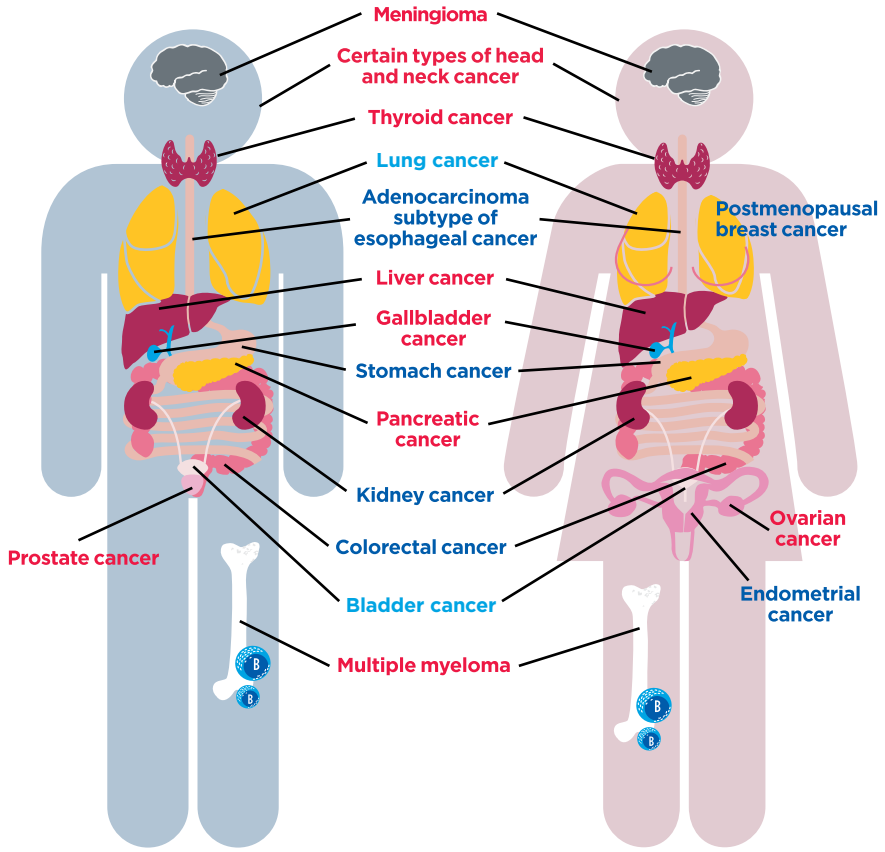
problems including type 2 diabetes, high blood pressure, heart disease, stroke, liver disease, and kidney disease (76).

Complex and interrelated factors ranging from socioeconomic and environmental influences to individual lifestyle factors contribute to obesity. There is, however, sufficient evidence that consumption of high-calorie, energy-dense food and beverages and insufficient physical activity play a significant role (76). In the United States, more than 5 percent of all newly diagnosed cancer cases among adults are attributable to eating a poor diet (80). Low intake of healthy foods such as whole grains, fruits, nuts, and seeds combined with the high intake of unhealthy foods such as sugar-sweetened drinks and high levels of red and processed meats are, in fact, responsible for one in five deaths globally (81).

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 (82). One initiative that has been effective in lowering the rates of obesity and severe obesity among children is the Special Supplemental Nutrition Program for Women Infants and Children (WIC) (83). Initiatives such as WIC are extremely important given that obesity during early childhood is associated with sustained overweight or obesity in adolescence and adulthood and that obesity during adolescence can increase the risk of developing cancer later in life (84-86).

FIGURE 4

REASONS TO MAINTAIN A HEALTHY WEIGHT AND STAY ACTIVE



Fifteen types of cancer —the adenocarcinoma subtype of esophageal cancer; certain types of head and neck cancer; advanced prostate cancer; meningioma; multiple myeloma; and colon, rectal, endometrial, gallbladder, kidney, liver, ovarian, pancreatic, stomach, thyroid, and postmenopausal breast cancers—have all been directly linked to being overweight or obese. Being physically active lowers the risk of eight cancers—esophageal, kidney, lung, stomach, colon, breast (postmenopausal), endometrial, and bladder (77-79). Cancers associated with obesity are shown in red; cancers associated with physical activity are shown in light blue; cancers that are associated with both are shown in dark blue.

Figure adapted from (36)

Another recent policy approach aimed at reducing obesity is the introduction of taxes on sugar-sweetened beverages in several local jurisdictions in the United States (87). Sugar-sweetened beverages are a major contributor to caloric intake among U.S. youth and adults (88)(89). Thus, it is encouraging that since the implementation of taxes on sugar-sweetened beverages, there are already some indications of reduction in consumption, especially in lower-income, racially and ethnically diverse neighborhoods (90)(91). However, ongoing research is needed to evaluate the long-term effects of these policies on obesity and obesity-related health outcomes such as cancer.

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

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

Maintain a healthy weight (body mass index [BMI] between 18.5 and 24.9) because 15 types of cancer have been causally linked to being obese or overweight (see **Figure 4,** p. 30).

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

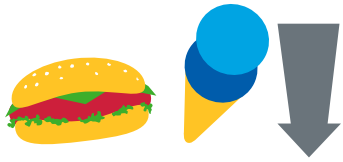
Be physically active as part of everyday life; regular physical activity can decrease risk for eight types of cancer (see **Figure 4,** p. 30, and sidebar on **Physical Activity Guidelines,** p. 32).

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

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

If consumed at at all, limit alcoholic drinks, because alcohol consumption can increase risk for six types of cancer (see **Figure 5,** p 33).

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



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

An estimated 2 percent of cancer deaths in the United States can be attributed to physical inactivity. Physical activity can reduce the risk of eight types of cancer (see **Figure 4,** p. 30). There is growing evidence that physical fitness may also reduce the risk of developing additional types of cancer (92). Furthermore, physical activity can dramatically lower rates of all-cause mortality after a diagnosis of certain types of cancer (see **Supporting Cancer Patients and Survivors,** p. 94). Considering this evidence, it is concerning that 35 percent of U.S. adults are physically inactive, and only a quarter of children and teenagers get the recommended hour of moderate-to-vigorous exercise a day (93-95). It is imperative that health care professionals and policy makers work together to increase awareness of the benefits of physical activity and support efforts to implement programs and policies to facilitate physical activity for all Americans (see sidebar on **Physical Activity Guidelines,** p. 32).

LIMIT ALCOHOL CONSUMPTION

Alcohol consumption has been causally linked with six different types of cancer (97) (see **Figure 5,** p. 33). Even modest use of alcohol may increase cancer risk, but the greatest risks are associated with excessive and/or long-term

PHYSICAL ACTIVITY GUIDELINES

About 80 percent of U.S. adults and adolescents are insufficiently active. The U.S. Department of Health and Human Services recommends the following minimum physical activity levels to improve the nation's health (96).

For preschool-age children (ages 3–5)

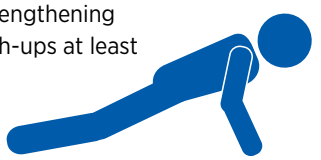
Physical activity throughout the day to enhance growth and development.

Adult caregivers should encourage active play that includes a variety of activities.

For school-age children and adolescents

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

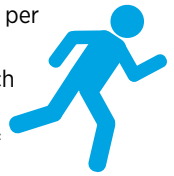
Muscle- and bone-strengthening exercises such as push-ups at least three days per week.



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

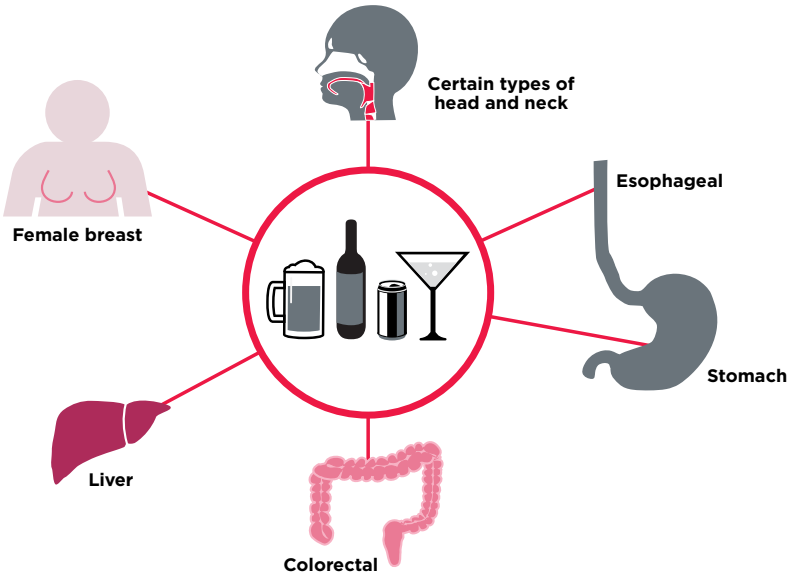
Older adults, those who are pregnant, and/or those with chronic health conditions and disabilities should consult their physicians and follow modified guidelines.

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

Adapted from (1)

FIGURE 5

ALCOHOL AND CANCER RISK



Consumption of alcohol increases an individual's risk of developing six types of cancer—certain types of head and neck cancer, esophageal squamous cell carcinoma, and breast, colorectal, liver, and stomach cancers (97).

consumption (98-101) (see sidebar on **Guidelines for Alcohol Consumption,** p. 34). Thus, it is concerning that in the United States, one in four adults binges on alcohol at least once a month (102). Researchers have identified multiple ways in which alcohol may increase the risk of cancer, including directly damaging cellular DNA and proteins through the production of toxic chemicals, once alcohol is metabolized after drinking (103).

Alcohol consumption accounted for 245,000 deaths from liver cancer globally in 2015 (106).

Beyond the United States, alcohol poses a significant public health challenge globally. In fact, alcohol-use disorders are now the most prevalent of all substance-use disorders worldwide (104), and in 2016, excessive use of alcohol resulted in 3 million deaths, including an estimated 0.4 million deaths from cancers (105). These data underscore the importance of adherence to comprehensive guidelines and 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

All three main types of skin cancer—basal cell carcinoma, squamous cell carcinoma, and melanoma, the deadliest form of skin cancer—are caused by exposure to UV radiation from the sun or indoor tanning devices. Sunburn, a clear indication of overexposure to UV radiation, is a preventable risk factor for skin cancer and those events occurring in childhood pose some of the greatest risk (107). Therefore,

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 (82):

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

Moderate drinking:

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

and only by adults of legal drinking age.

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

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

Heavy drinking:

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

Binge drinking:

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

Excessive alcohol consumption, which includes binge drinking, heavy drinking, and any drinking by pregnant women or those under 21 years of age, 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 age 18 and older for alcohol misuse and provide persons engaged in excessive drinking with brief behavioral counseling interventions.

Adapted from (7)

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. 35).

In the United States, melanoma incidence among non-Hispanic whites continues to rise, particularly in individuals older than 55 (110). To break the current trend, we need to establish skin cancer prevention as a national priority. In an effort to achieve this goal, the U.S. Surgeon General released a call to action to prevent skin cancer in 2014 (111). Since its release, multiple sectors including health care, government, business, advocacy, and communities have coordinated efforts and made major strides toward reducing exposure. As a result, indoor tanning among U.S. youth and adults has declined significantly (112)(113). However, even in 2015, more than 35 percent of adults reported experiencing sunburns either through outdoor exposure or indoor tanning (47). Furthermore, according to a recent survey, even though 68 percent of Americans know that skin cancer is the most common cancer in the United States, only 42 percent put sunscreen on parts of their body exposed to the sun (114). Continued efforts from all sectors are necessary to identify and implement more effective interventions to promote sun-safe behavior and reduce the burden of skin cancer.

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.);

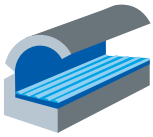
wear clothing that covers your arms and legs; some clothing is designed to provide protection from the sun;

wear a wide-brimmed hat;

wear wrap-around sunglasses;

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

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



The U.S. Preventive Services Task Force (USPSTF), an independent, volunteer panel of experts in prevention and evidence-based medicine, recommends that clinicians counsel their fair-skinned patients ages 6 months to 24 years—or their parents—on limiting exposure to ultraviolet (UV) radiation to lower skin cancer risk (108).

Adapted from (109)

While less common than in Caucasians, individuals of other racial/ethnic backgrounds can get skin cancers (115)(116). In fact, skin cancer represents approximately:

2-4% of all cancers in Asians.

4-5% of all cancers in Hispanics.

1-2% of all cancers in blacks.

PREVENT AND ELIMINATE INFECTION WITH CANCER-CAUSING PATHOGENS

Persistent infection with several pathogens including the human papillomavirus (HPV), hepatitis B virus (HBV), hepatitis C virus (HCV), and *Helicobacter pylori* is known to cause cancer (see **Table 3,** p. 36). In the United States, in 2014, about 3 percent of all cancer cases and cancer deaths were attributable to infection with pathogens (46). Individuals, therefore, can significantly lower their risks by protecting themselves from infection or by obtaining treatment, if available, to eliminate an infection (see sidebar on **Preventing or Eliminating Infection with the Four Main Cancer-causing Pathogens,** p. 37).

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 United States Preventive Services Task Force (USPSTF) recommend one-time HCV testing for baby boomers, recent data show that only 14 percent of adults in this population group have been tested (117). Given that in the U.S., liver cancer incidence is increasing rapidly and that infection with HBV or HCV accounts for 65 percent of liver cancers, more effective

TABLE 3

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	

VIRUSES

Infectious Agent	Cancer	% of global cancer cases attributable to infection*
Epstein-Barr virus (EBV)	Hodgkin and certain non-Hodgkin lymphomas, 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	

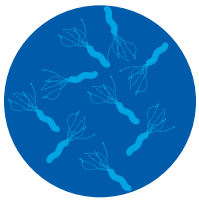
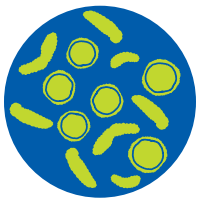
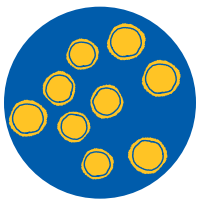
* Where known

Adapted from (36)

implementation of vaccination, screening, and treatment is needed urgently to significantly reduce the burden of this disease (118). In this regard, a recent initiative that is aimed to reduce the burden of HCV infection is the recommendation from the Indian Health Service for universal screening of all American Indian and Alaska Native (AI/AN) adults (https://www.ihs.gov/ihm/sgm/). Among AI/AN, HCV infections occur earlier than in the general population and HCV-related deaths are double the national rate (119).

It is estimated that in the United States, HPV infection accounts for nearly 34,000 cancers each year including almost all cervical and anal cancers as well as the majority of vaginal, vulvar, penile, and oropharyngeal cancers (120). HPV vaccines are highly effective and can prevent up to 90 percent of HPV-related cancers. In fact, since the introduction of HPV vaccines in the United States, the rates of vaccine-targeted cervical HPV infection have declined, and early evidence suggests declines in incidence of cervical precancer and cancer among young females (121-125). Despite the clear effectiveness of HPV vaccines, in 2018, only 54 percent of girls and 49percent of boys were up to date with the recommended vaccination regimen (52). Although these numbers show slight improvement over earlier years, vaccination

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-stage gastric cancer that has been surgically treated
Hepatitis B virus (HBV) 	• HBV vaccination • Avoid behaviors that can transmit infection (e.g., injection drug use and unsafe sex)	Treatment of those chronically infected with antiviral drugs rarely eliminates infection but does slow virus multiplication; this slows the pace at which liver damage occurs and thereby reduces risk for liver cancer	• Vaccination part of childhood immunization schedule since 1991 • CDC and USPSTF recommend screening high-risk individuals—those from countries with high rates of HBV infection, HIV-positive persons, injection drug users, household contacts of HBV-infected individuals, and men who have sex with men—for HBV infection
Hepatitis C virus (HCV) 	Avoid behaviors that can transmit infection (e.g., injection drug use and unsafe sex)	Treatment with any of several antiviral drugs can eliminate infection	CDC and USPSTF recommend screening those born from 1945 to 1965 for HCV infection
Human papillomavirus (HPV) 	• Three FDA-approved vaccines • Practice safe sex, although this may not fully protect against infection	None available	CDC recommends HPV vaccination for boys and girls age 11 or 12; recommendations for other groups can be found in the sidebar on **HPV Vaccination Recommendations**, see p. 38)

CDC, Centers for Disease Control and Prevention; MALT, mucosa-associated lymphoid tissue; USPSTF, U.S. Preventive Services Task Force.
Adapted from (109)

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 males and females ages 9 to 45.

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

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

rates in the United States are much lower than they are in other developed countries such as Australia where high uptake (above 70 percent) is predicted to eliminate cervical cancer as a public health concern within the next 20 years (126).

Until recently, cervical cancer was the most common HPV-related cancer in the United States. However, the incidence of HPV-related oropharyngeal cancer has been increasing, mostly among men, while the incidence of cervical cancer has been declining and oropharyngeal squamous cell carcinoma was recently reported to have become the most common HPV-associated cancer in the United States (121). There are, however, no formal screening tests for oropharyngeal squamous cell carcinoma. Therefore, developing effective strategies to increase the uptake of HPV vaccines, such as those detailed in the recent report from the U.S. President's Cancer Panel, could have immense public health benefit (120).

High coverage of HPV vaccination and cervical screening, globally, from 2020 onwards, could prevent nearly 13 million cervical cancer cases over the next 50 years, and eliminate cervical cancer as a public health problem by 2099 (127).

BE COGNIZANT OF REPRODUCTIVE AND HORMONAL INFLUENCES

BREASTFEEDING

There is strong evidence that breastfeeding decreases the risk of breast cancer in the mother (128). Women who breastfeed have a lower risk of a particularly aggressive type of breast cancer known as triple-negative breast cancer (129). According to recent data (130), breastfeeding is associated with a 22 percent reduction in the risk of developing triple-negative breast cancer, whereas weaker or no correlations have been observed with other types of breast cancer. Increasing awareness of this information among African American women may be particularly important because African American women have a disproportionately high incidence of triple-negative breast cancer and a lower prevalence of breastfeeding compared to all other U.S. racial and ethnic groups (131).

HORMONE REPLACEMENT THERAPY

Hormone replacement therapy (HRT) refers to treatments that aim to relieve the common symptoms of menopause and the long-term biological changes, such as bone loss, that occur after menopause due to declining levels of the hormones estrogen and progesterone in a woman's body. HRT usually involves treatment with estrogen alone or estrogen in combination with progestin, a synthetic hormone like progesterone.

Women who have a uterus are prescribed estrogen plus progestin. This is because estrogen alone, but not in combination with progestin, is associated with an increased risk of endometrial cancer, a type of cancer that forms in the tissue lining the uterus. Estrogen alone is used only in women who have had their uteruses removed.

The most comprehensive evidence about the health effects of HRT was obtained from clinical trials conducted by the NIH as part of the Women's Health Initiative. The data indicated that women who use estrogen plus progestin have an increased risk of developing breast cancer (132). The risk is greater with longer duration of use but decreases significantly following cessation (133). The increased risks have been observed both for white and black women (134) (135). Therefore, individuals who are seeking relief from menopausal symptoms should discuss with their health care providers the advantages and possible risks of using HRT before making a decision about what is right for them.

LIMIT EXPOSURE TO ENVIRONMENTAL CARCINOGENS

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 (136). Other examples of environmental carcinogens include asbestos, lead, radiation, and benzene. According to the World Health Organization (WHO), environmental risk factors account for nearly 20 percent of all cancers, globally, most of which occur in low- and middle-income countries.

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

One environmental pollutant that was classified by the International Agency for Research on Cancer (IARC), an affiliate of the WHO, as having the ability to cause cancer in humans, is outdoor air pollution (137). Two types of air pollution are most common in the United States, ozone and particle pollution. Particle pollution refers to a mix of tiny solid and liquid particles that are in the air we breathe, and in 2013, IARC concluded that particle pollution may cause lung cancer (138). Therefore, it is concerning that from 2015 to 2017, nearly 20 million people in the United States were exposed year-round to unhealthy levels of particle pollution. New policy efforts to reduce the release of pollutants into the atmosphere are needed if we are to reduce the burden of cancer.

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. 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.

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 (breast, cervical, colorectal, and prostate) for which screening tests have been used to screen large segments of the U.S. population who are at average risk of developing the cancer being screened for.
- Every person has a unique risk for each type of cancer based on genetic, molecular, and cellular makeup, lifetime exposures to cancer risk factors, and general health.
- We need to develop new strategies to ensure optimal uptake of cancer screening by all.

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

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 precancerous lesions or cancers at an early stage of development (see **Figure 6,** p. 41). If precancerous lesions are detected, they can be treated or surgically removed before they become cancers. Finding cancer early, before it has spread to other parts of the body, makes it more likely that a patient can be treated successfully. Treating or surgically removing a precancerous lesion or early-stage cancer is called cancer interception.

WHAT IS CANCER SCREENING AND HOW IS IT DONE?

Screening for cancer means checking for precancerous lesions or cancer in people who have no signs or symptoms of the cancer for which they are being checked. The aim is to find the abnormality at the earliest possible stage because this increases the likelihood that the patient can be treated successfully, as highlighted by the fact that patients diagnosed with colorectal cancer that is confined to the colon or rectum have a 5-year relative survival rate of 90 percent, while those diagnosed with colorectal cancer that has metastasized have a 5-year relative survival rate of 14 percent (8).

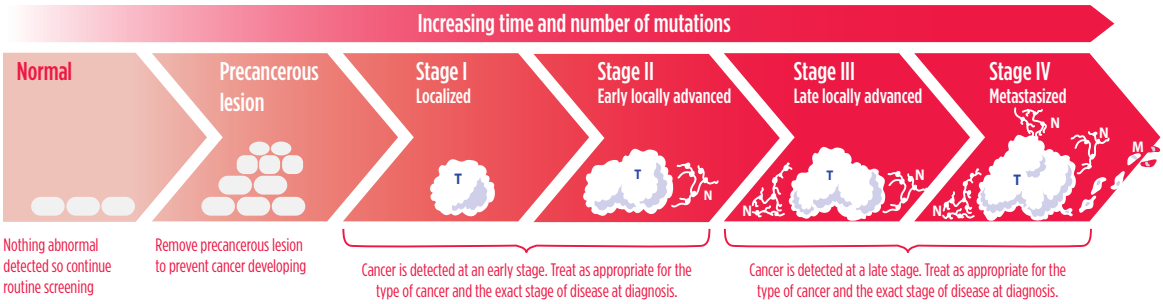
Screening for cancer can be done in various ways, including by using imaging technologies to look for abnormalities inside the body, and by collecting tissue or fluid samples and then analyzing them for abnormalities characteristic of the cancer being screened for (see sidebar on **How Can We Screen for Cancer?** p. 42).

CONSENSUS ON CANCER SCREENING

Screening for cancer has many benefits, but it also has the potential to cause unintended harms (see sidebar on **Cancer Screening,** p. 43). This is why cancer screening is not recommended for everyone. Determining whether and for whom a cancer screening test can provide benefits that outweigh the potential harms requires extensive research and careful analysis of the data generated.

FIGURE 6

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 genetic 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 predicted based on the finding. For example, the screening test may show that there is no abnormality present; in this situation, the person should continue routine screening. The test may detect a precancerous lesion, which can be removed or treated; in this situation, the screen has led to the prevention of a cancerous lesion developing. The test may find a cancer at an early stage of development, stage I or stage II, before it has spread and at a point at which it is more likely that the patient can be treated successfully. It also may find a cancer at a late stage of development, stage III or stage IV, when treatment is less likely to be curative. Treating or surgically removing a precancerous lesion or treating early-stage cancer is called cancer interception.

Adapted from (109)

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 harms of cancer screening tests to make evidence-based recommendations about the use of these tests. These volunteer experts form the 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.

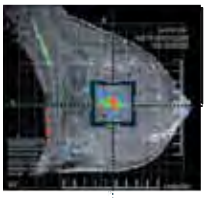
In addition to considering evidence regarding potential new screening programs, the USPSTF re-evaluates existing recommendations as new research becomes available and can revise the recommendations if necessary. For example, the USPSTF revised its recommendations for cervical cancer screening in August 2018 (139). The revision added HPV testing alone every 5 years as a third screening option for women ages 30 to 65 who are at average risk of developing cervical cancer.

Many professional societies also convene panels of experts to evaluate data regarding the benefits and potential harms 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 harms than other groups do, this can result in differences in recommendations from distinct groups of experts. The differences highlight areas in

HOW CAN WE SCREEN FOR CANCER?

Highlighted here are some of the most commonly used cancer screening tests. When to use these tests and in whom is discussed elsewhere (see Consensus on Cancer Screening, p. 40).

Breast Cancer



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

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

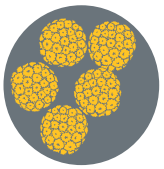
In most cases, the image is 2-dimensional, but some machines generate 3-dimensional images in a process called breast tomosynthesis.

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

Cervical Cancer

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

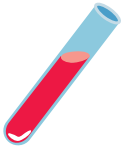
Can detect precancerous or cancerous cervical lesions, but the aim of screening is to find them at the earliest possible stage.



HPV test: Detects the presence of certain cervical cancer–causing types of human papillomavirus (HPV).

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

Prostate Cancer



PSA test: Measures the level of a protein called prostate-specific antigen (PSA) in blood.

Does not directly detect prostate cancer, but the blood level of PSA is often elevated in men with prostate cancer. Thus, the test identifies men for whom further testing is recommended.

Colorectal Cancer

Stool tests: Some test for the presence of red blood cells in stool samples. Others test for both red blood cells and certain genetic mutations linked to colorectal cancer.

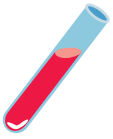
Do not directly detect colorectal precancerous lesions or cancers, but identify people for whom further testing is recommended.

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

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

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

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



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

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

Lung Cancer

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

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

Adapted from (109)

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 6,** p. 41).

Reduced incidence of advanced disease. Screening tests that detect cancers at an early stage of development can reduce the individual's risk of being diagnosed with the screened cancer at a stage when it has spread to other parts of the body (see **Figure 6,** p. 41).

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.

Potential Harms of Screening

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

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

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

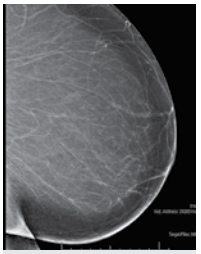
False-negative test results. Not all individuals who have a negative screening test result are free from the screened cancer. The rates of false-negative test results are generally low, but a false-negative test result can lead to missed opportunities for early treatment.

Overdiagnosis and overtreatment. Not all precancerous lesions or cancers detected by screening will go on to cause symptoms and threaten life. Overdiagnosis, as this is called, can lead to overtreatment, which carries its own potential harms and costs. The rates of overdiagnosis and overtreatment vary among cancer types. More longitudinal studies to elucidate and quantify the impact of overdiagnosis and overtreatment are required. Additional research is also needed to determine ways to identify which of the early-stage cancers detected through screening are most likely to go on to cause symptoms and threaten life.

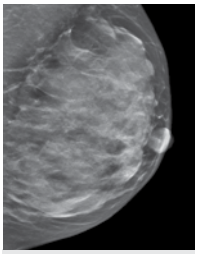
Adapted from (1)

BREAST DENSITY

What Is Breast Density?



Nondense breast



Dense breast

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

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

The last two categories are considered dense breasts.

Why Is Breast Density Important?

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

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

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

Many U.S. states have enacted legislation mandating that women who have a mammogram 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
Adapted from (7)

which more research is needed to determine definitively the relative benefits and potential harms of screening, to develop new screening tests that have clearer benefits and/or lower potential harms, or to better identify people for whom the benefits of screening outweigh the potential harms.

Even though there is more consensus than disagreement among cancer screening recommendations from different groups of experts, it can still be challenging for individuals to ascertain for which cancers to be screened and when. One of the most important factors people should consider when making decisions about cancer screening is their own risk of the cancer for which they are being screened. Recommendations for individuals at average risk of developing a certain cancer are different from those for individuals at increased risk of developing the same cancer. Therefore, individuals should consult with their health care providers to develop a cancer screening plan that is tailored to their own unique cancer risks, general health, and tolerance for the potential harms of a screening test.

Each person's unique cancer risks are determined by numerous factors, including genetic, molecular, cellular, and tissue makeup (see sidebar on **Breast Density**), lifetime exposures to cancer risk factors, and general health. 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 Cancer Screening Recommendations for Average-risk Individuals,** p. 45). Age is an important risk factor for cancer because cancer is predominantly a disease of aging—91 percent of U.S. cancer diagnoses occur among those age 45 and older (8). Thus, a person's risk for most types of cancer increases with age.

CONSENSUS 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 of developing the cancers being screened for. Here, we highlight consensus, as of July 31, 2019, 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 Urologists Association (AUA). Not all of the professional societies have recommendations for every cancer screening test.

Breast Cancer Screening

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

Some recommend starting regular screening mammograms before age 50. It is important to note, however, that all the groups support women ages 40–49 having the opportunity to have regular screening mammograms if they decide it is right for them.

Cervical Cancer Screening

There is consensus among the ACOG, 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, a Pap test and human papillomavirus (HPV) testing every 5 years, or HPV testing alone every 5 years; and
- women older than 65 should not be screened if they are at average risk of the disease because they have previously had regular screenings with normal results and are not otherwise at high risk of developing cervical cancer.

Colorectal Cancer Screening

There is consensus among the ACS, ACP, NCCN, and USPSTF that adults ages 50–75 who are at average risk of developing colorectal cancer should be screened. How often a person should be screened depends on the screening test used (see sidebar on **How Can We Screen for Cancer?** p. 42).

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 their health care providers 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 of developing prostate cancer talk to a physician about the benefits and potential harms of prostate specific antigen (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 the cancers highlighted here. 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).

In addition to age, a person's other risks of developing cancer can change over the course of a lifetime; for example, a woman whose screening mammogram leads to a breast biopsy that reveals certain noncancerous breast conditions, such as lobular carcinoma in situ, is now at increased risk of developing breast cancer and should consider taking measures to reduce her breast cancer risk, such as taking a preventive medicine. Therefore, it is important that individuals maintain a dialog with their health care providers and continually evaluate their cancer screening plans, updating them if necessary.

Some individuals are at increased risk of developing a certain type or types of cancer because of their exposure to modifiable cancer risk factors (see **Preventing Cancer: Identifying Risk Factors,** p. 24). For example, people who smoke cigarettes are 15 to 30 times more likely to develop lung cancer than people who do not smoke cigarettes (140)(141). Others are at increased risk because they inherited a cancer-predisposing genetic mutation (see **Table 2,** p. 21). People who have a family or personal history of cancer and think that they are at high risk for inheriting such a mutation should consult their health care providers and consider genetic testing (see sidebar on **How Do I Know If I Am at High Risk for Developing an Inherited Cancer?**). As researchers learn more about inherited cancer risk (142-144), there will be new genetic mutations to test for and changes to the recommendations about who should be offered genetic testing. Thus, it is important that individuals at high risk for inheriting a cancer-predisposing genetic mutation maintain an ongoing dialog with their health care providers and continually evaluate whether genetic testing is available and/or right for them.

It is important to note that there are direct-to-consumer genetic tests that individuals can use without a prescription from a physician, but there are many factors to weigh when considering whether to use one of these tests. Because of the complexities of these tests, the FDA and Federal Trade Commission recommend involving a health care professional in any decision to use such testing, as well as to interpret the results.

All people who have an increased risk of developing a certain type or types of cancer should consult with their health care providers to tailor risk-reducing measures to their personal situations. Some individuals may be able to reduce their risk by increasing their use of certain cancer screening tests or using cancer screening tests that are not recommended for people who are at average risk for the cancer (see sidebar on **Consensus Cancer Screening Recommendations for High-risk Individuals,** p. 47). Others may consider having risk-reducing surgery or taking a preventive medicine, for example, women at high risk for breast cancer may take tamoxifen or raloxifene to reduce their risk (see **Table 4,** p. 48, and **Supplemental Table 1,** p. 142).

As we increase our understanding of the biology of pre-cancerous and cancerous lesions we will be able to identify new biomarkers and develop new screening tests for more types of cancer (146)(147). 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 (148)(149).

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 you have one or more of the following (145):

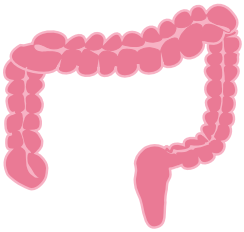
- several close blood relatives with the same type of cancer, such as a mother, daughter, and sisters with breast cancer;
- family members diagnosed with cancers at younger ages than usual, such as colon cancer in a 20-year-old;
- one or more family members who have more than one type of cancer, such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

USE OF CANCER SCREENING IS SUBOPTIMAL

Even though the benefits of breast, cervical, colorectal, and lung cancer screening outweigh the potential risks for defined groups of individuals (see sidebars on **Consensus Cancer**

CONSENSUS CANCER SCREENING RECOMMENDATIONS FOR HIGH-RISK INDIVIDUALS

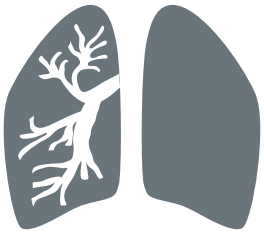
The U.S. Preventive Services Task Force (USPSTF) and many professional societies have evidence-based recommendations about the use of cancer screening tests among individuals who are at increased risk of developing the cancer(s) being screened for. Here, we highlight some examples of recommendations for cancer screening for some of these individuals, as of July 31, 2019, from the USPSTF, the American Cancer Society (ACS), the National Comprehensive Cancer Network (NCCN), and the United States Multi-Society Task Force (MSTF) on colorectal cancer.



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 (see sidebar on **How Can We Screen for Cancer?** p. 42). For example:

- the NCCN and MSTP on colorectal cancer recommend that individuals at high risk because they inherited a genetic mutation that causes Lynch syndrome (see **Table 2,** p. 21) 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 ACS, NCCN, and MSTP on colorectal cancer recommend that individuals at increased risk because they have a first-degree relative who has been diagnosed with colorectal cancer should start screening with colonoscopy at age 40 or 10 years before the youngest case was diagnosed, whichever is earlier; and,
- the MSTP on colorectal cancer recommends that because African Americans are at increased risk for colorectal cancer they should begin screening at age 45.



Lung Cancer

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

Screening Recommendations for Average-risk Individuals, p. 45, and **Consensus Cancer Screening Recommendations for High-risk Individuals**), many people for whom screening is recommended do not get screened (see sidebar on **Suboptimal Use of Cancer Screening Tests,** p. 48) (150)(151). Individuals who are not up to date with cancer screening recommendations are disproportionately found in segments of the U.S. population that are medically underserved (152) (153)(see sidebars on **Disparities in Cancer Screening,** and **Which U.S. Population Groups Experience Cancer Health Disparities?** p. 49 and p. 13).

In addition to suboptimal uptake among those individuals for whom screening is recommended, some people for whom screening is not recommended, such as adults above the recommended age cutoff for a given cancer screening test and those with limiting life expectancy, are screened even though the evidence indicates that the benefits of screening are unlikely to outweigh the potential harms for them (154-156).

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

TABLE 4

SURGERIES FOR THE PREVENTION OF CANCER

GENETIC MUTATION	CANCER	TECHNIQUE	REMOVES
APC	Colon cancer	Colectomy	Colon/large intestine
BRCA1 or *BRCA2*	Breast and ovarian cancers	Mastectomy and salpingo-oophorectomy	Breasts, and ovaries and fallopian tubes
CDH1	Breast and stomach cancers	Mastectomy and gastrectomy	Breast and stomach
Mutations associated with Lynch syndrome	Colon, endometrial, and ovarian cancers	Colectomy, hysterectomy, and salpingo-oophorectomy	Colon/large intestine, uterus, and ovaries and fallopian tubes
RET	Medullary thyroid cancer	Thyroidectomy	Thyroid

SUBOPTIMAL USE OF CANCER SCREENING TESTS

Not all individuals for whom cancer screening is recommended are up to date with the screening recommendations (see sidebar on **Consensus Cancer Screening Recommendations for Average-risk Individuals** and **Consensus Cancer Screening Recommendations for High-risk Individuals,** p. 45 and p. 47). For example, a substantial percentage of individuals for whom the U.S. Preventive Services Task Force (USPSTF) recommended breast, cervical, colorectal, and lung cancer screening were not up to date with screening in 2015, which is the last year for which these data are currently available (150)(151):

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.

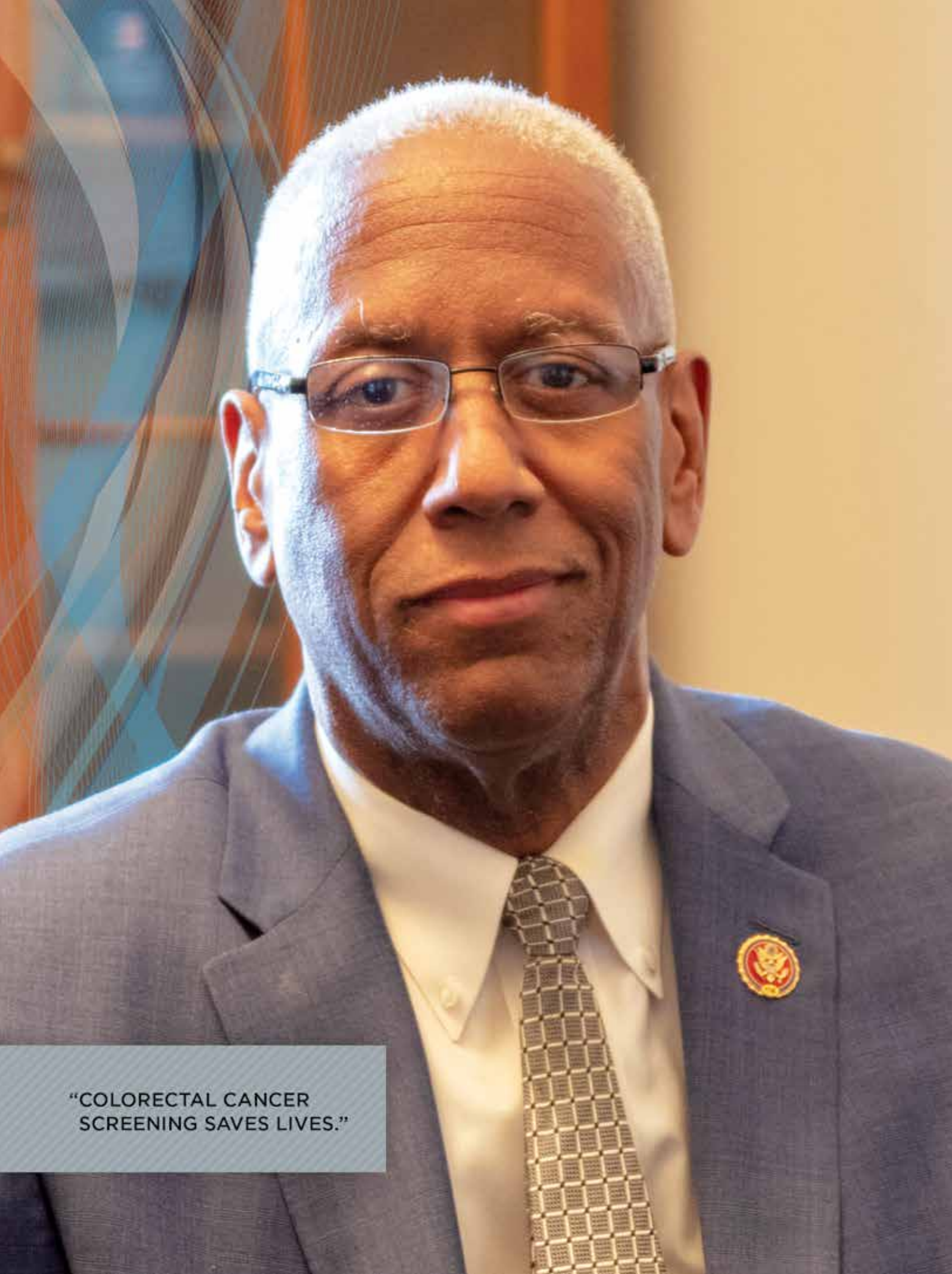
96% of adults ages 55–80 who have smoked at least one pack of cigarettes per day for 30 years, or the equivalent (two packs per day for 15 years, etc.), and who currently smoke or have quit within the past 15 years were not up to date with lung cancer screening.

DISPARITIES IN CANCER SCREENING

There are disparities in adherence to U.S. Preventive Services Task Force cancer screening recommendations among certain segments of the U.S. population. These disparities, which are a result of complex and interrelated factors (see sidebar **Why Do U.S. Cancer Health Disparities Exist?** p. 15), include the following (153)(154):

SIGNIFICANTLY MORE LIKELY	
70.4% VERSUS **53.4%**	Whites are significantly more likely to be up to date with colorectal cancer screening than Hispanics, 70.4% versus 53.4%.
70% VERSUS **34%**	Adults who have health insurance are significantly more likely to be up to date with colorectal cancer screening than adults who are uninsured, 70.0% versus 34.0%.
77.3% VERSUS **64.1%**	Women in the highest income bracket are significantly more likely to be up to date with breast cancer screening than women in the lowest income bracket, 77.3% versus 64.1%.
77.2% VERSUS **45.7%**	Women who report having a personal doctor are significantly more likely than women who report having no doctor to be up to date with breast cancer screening, 77.2% versus 45.7%.
82.5% VERSUS **69%**	Straight women are significantly more likely to be up to date with cervical cancer screening than lesbian or gay women, 82.5% versus 69.0%.
76% VERSUS **58%**	Adults in Massachusetts are significantly more likely to be up to date with cervical cancer screening than those in Wyoming, 76% versus 58%.

certain segments of the U.S. population highlight the need for new strategies, legislation, and public policies to increase cancer screening awareness, access, and uptake among those for whom screening is recommended, as discussed by **Congressman Donald McEachin** (see p. 50). Identifying strategies to achieve this goal is an area of intensive research investigation. Numerous studies have shown that colorectal cancer screening rates can be significantly increased by actively reaching out to adults not up to date with screening either by mailing then information about colorectal cancer risk and a stool test or by implementing patient navigation programs that provide individualized assistance to help patients overcome personal and health care system barriers, and to facilitate understanding and timely access to screening (157)(158). Regular, high-quality patient–health care provider conversations offer another way to increase awareness and ensure optimal implementation of cancer screening. However, recent research suggests that we need to do much more to increase the frequency and the quality of these conversations (154-160).


"COLORECTAL CANCER
SCREENING SAVES LIVES."

THE HONORABLE
DONALD MCEACHIN

AGE 57 | U.S. REPRESENTATIVE FOR VIRGINIA'S 4TH CONGRESSIONAL DISTRICT

WORKING TO REMOVE BARRIERS TO COLORECTAL CANCER SCREENING

Colorectal cancer screening saves lives. I know this because it saved mine. That is why I am dedicated to increasing awareness of and removing barriers to colorectal cancer screening. It is also why I am highly cognizant of the need for greater investment in cancer research. Whether it is the research focused on cancer prevention, early detection, treatment, or cure, the value of each federal dollar spent on research is immeasurable.

A routine colonoscopy led to my diagnosis with rectal cancer in 2014. I was devastated. I thought the future I had imagined was gone; I particularly remember thinking that I would lose the opportunity to dance at my children's weddings. However, I was blessed because the cancer was caught at an early stage, before it spread to my lymph nodes or other parts of my body, and my treatment—a combination of surgery, radiation, and chemotherapy—was successful. I have been cancer-free ever since, and I am delighted to say that I got to dance at my son's wedding this past October.

My experience with cancer provides me with deep insight into a number of health care–related issues and informs my work as a lawmaker.

One issue that I am passionate about is reducing the burden of colorectal cancer, which is the second leading cause of cancer death for men and women combined in the United States. In 2019 alone, approximately 51,000 Americans will die from the disease. We already have the tools to prevent many colorectal cancer deaths through early detection and removal of tissue that could become cancerous: preventive colorectal cancer screening colonoscopies. However, about one-third of all U.S. adults for whom colorectal cancer screening is recommended are not up to date with their screenings. The situation is even worse if we consider only African Americans, Hispanics, those who are uninsured, those who have public health insurance, or those who live in poverty. Therefore, we must make colorectal cancer screening more accessible to all.

One financial barrier to screening colonoscopies faced by Medicare beneficiaries is that Medicare currently does not pay the copay for the removal of a polyp(s) during a screening colonoscopy. The bipartisan, bicameral "Removing Barriers to Colorectal Cancer Screening Act of 2019," which I proudly introduced together with Congressman Donald Payne, Jr. (D-NJ), Congressman Rodney Davis (R-IL), and Congressman David McKinley, (R-WV), will eliminate this potential cost if it is enacted, making lifesaving colorectal cancer screening colonoscopies more accessible to Medicare beneficiaries.

My experience with cancer also made me acutely aware of the emotional, mental, and physical toll that cancer has on a person and his or her family. One worry that many cancer patients and families face is whether they can afford the treatments that will keep them alive. That is why I am delighted that the House Energy and Commerce Committee, of which I am a member, has made lowering prescription drug prices a top health priority.

In addition, my appreciation of the vital importance of federal investment in cancer research has been increased by my experience with cancer. In fact, funding from the National Institutes of Health, which is provided by the federal government, contributed in some way to the development of every single one of the 210 drugs approved by the U.S. Food and Drug Administration between 2010 and 2016, including numerous breakthrough drugs to combat cancer.

Our country has led the charge in eradicating polio, smallpox, and measles, and, in part because of federal funding, we have begun to make metastatic cancer chronic, not fatal. We still have far to go, but we must continue to build on the progress we have already made, and I am committed to doing all that I can to ensure Congress makes federal funding for cancer research a priority.

TRANSFORMING LIVES THROUGH INNOVATIVE CANCER SCIENCE

IN THIS SECTION, YOU WILL LEARN:

- Research that increases our understanding of the genetic, molecular, and cellular characteristics of cancer is continuing to spur advances in the treatment of cancer.
- Advances are being made across all five pillars of cancer care: surgery, radiation, cytotoxic chemotherapy, molecularly targeted therapy, and immunotherapy.
- From August 1, 2018 to July 31, 2019, the FDA approved 17 new therapeutics for treating patients with certain types of cancer.
- During the same period, the uses of 10 previously approved anticancer therapeutics were expanded by the FDA to include the treatment of additional types of cancer.

Progress across the continuum of clinical cancer care improves survival and quality of life for people around the world. The progress is driven by the dedicated efforts of individuals working throughout the cycle of medical research (see **Figure 7,** p. 53).

MEDICAL RESEARCH

Medical research is an iterative cycle (see **Figure 7,** p. 53). Each discovery builds on knowledge gained from prior research. The 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 medical research or clinical practice (see sidebar on **What Is Medical Research?** p. 54). The discoveries lead to hypotheses that are tested by researchers performing experiments in a wide range of models that mimic healthy and diseased conditions. Results from these experiments can lead to the identification of a potential preventive intervention or therapeutic target, or to the identification of a potential predictive or prognostic biomarker. They also can feed back into the cycle by providing new discoveries that lead to more hypotheses.

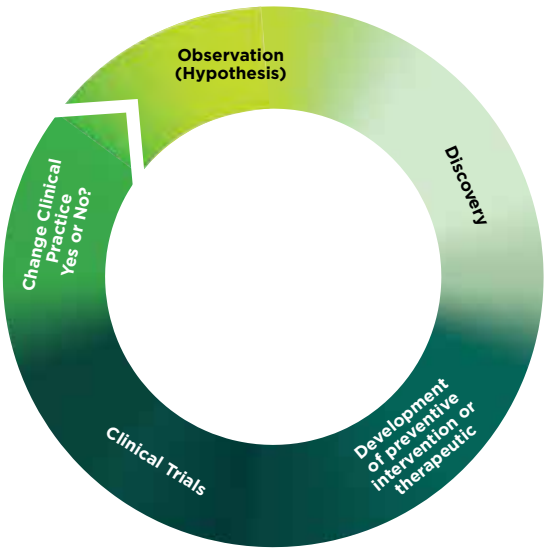
After a potential therapeutic target is identified, it takes many more years of preclinical research before a candidate therapeutic is developed and ready for testing in clinical trials (see sidebar on **Therapeutic Development,** p. 55). During this time, candidates are rigorously tested to identify potential toxicities and to determine the appropriate doses and dosing schedules for testing in the first clinical trial.

Before candidate therapeutics can be approved by the FDA and used as part of patient care, the safety and efficacy of the agents must be rigorously tested through clinical trials. All clinical trials are reviewed and approved by institutional review boards before they can begin and are 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.

Clinical trials that test candidate therapeutics for patients with cancer have traditionally been done in three successive phases (see **Figure 8,** p. 56). However, the multiphase clinical testing process requires a large number of patients and takes many years to complete, making it extremely costly and one of the barriers to rapid translation of scientific knowledge into clinical advances. One recent report estimated that the average time from patent filing through clinical development and FDA approval to market launch

FIGURE 7

THE MEDICAL RESEARCH CYCLE



Results from any type of research can fuel the medical research cycle by providing observations relevant to the practice of medicine, which lead to questions, or hypotheses, that are tested in experiments during the discovery phase of research. During the discovery phase, traits unique to a disease may be uncovered, leading to the development of a potential therapeutic (see sidebar on **Therapeutic Development,** p. 55). Before entering clinical testing, potential therapeutics undergo preclinical testing to identify any toxicities and help determine initial dosing. The safety and efficacy of potential therapeutics are then tested in clinical trials. If an agent is safe and 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 therapeutic can feed back into the medical research cycle and further enhance the use of that agent or the development of others like it. If, however, a therapeutic is not safe or effective and fails to gain FDA approval, the observations from the clinical testing still feed back into the medical research cycle to spur future research efforts. Because the cycle is iterative, it is constantly building on prior knowledge, and research undertaken during any part of the cycle continually powers new observations.

Figure adapted from (36)

was 13.6 years for the 59 new therapeutics approved by the FDA in 2018, of which 16 were new therapeutics for patients with cancer (161). Another study estimated that the median time it takes to complete the multiphase clinical testing process for anticancer therapeutics is 13.1 years (162).

Over the past three decades, the FDA implemented several changes that have altered how clinical trials can be conducted and reviewed in an effort to reduce the length of time it takes to obtain a clear result from a clinical trial, including developing four evidence-based strategies to expedite assessment of therapeutics for life-threatening diseases such as cancer. Two of these strategies, accelerated approval and breakthrough therapy designation, were recently shown to be working as intended: the average time from patent filing to launch for therapeutics approved using the accelerated approval and breakthrough therapy designation strategies was 15 percent and 19 percent shorter, respectively, than it was for therapeutics approved without using these strategies (161). This progress in FDA assessment of new therapeutics is highly relevant to patients with cancer because most anticancer therapeutics are approved using one or more of the four expedited strategies. For example, of the 17 new anticancer therapeutics approved by the FDA during the 12 months spanning this report, 16 were approved using one of the four expedited review strategies, including nine that were approved using the accelerated approval and/or breakthrough therapy designation strategies.

In addition, advances in our understanding of cancer biology have enabled researchers, regulators, and representatives of the pharmaceutical industry to develop new ways of designing and conducting clinical trials. Among the new ways to design clinical trials that have emerged in recent years are adaptive, seamless, and master protocol designs (163-165). These designs aim to streamline the clinical development of new anticancer

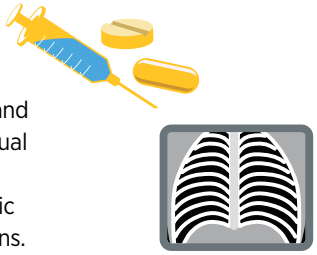
WHAT IS MEDICAL RESEARCH?

Medical research is sometimes refered to as biomedical research, as defined by the Organization for Economic Cooperation and Development (OECD), 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.



Any individual whose work falls within the definition of medical research is part of the medical research community. Thus, the medical research community is highly diverse. It includes, but is not limited to, basic, translational, and clinical researchers working in a wide range of disciplines, including biology, chemistry, immunology, physics, engineering, and computer science; physician-scientists; health care providers; and population scientists.

Adapted from (36)

DISPARITIES IN CLINICAL TRIAL PARTICIPATION

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

Non-Hispanic black men account for about 17 percent of new prostate cancer cases, but only constituted 6 percent of the participants in the clinical trials that led to the approval of apalutamide (Erleada), a relatively new treatment for prostate cancer (2)(175)(176).

Adults age 65 or older account for about two-thirds of patients with breast, lung, colorectal, and prostate cancer, but account for only one-third of participants in clinical trials testing treatments for these four types of cancer (170).

Hispanic children with cancer are more than 50 percent less likely to enroll in clinical trials testing treatments for childhood cancer compared with non-Hispanic white children (171).

therapeutics by matching the right therapeutics with the right patients earlier, reducing the number of patients who need to be enrolled in the trial before it is determined whether the anticancer therapeutic being evaluated is safe and 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 (165). The emergence of this clinical trial design has largely been driven by our increased understanding of the genetic mutations that underpin cancer initiation and growth. "Basket trials" are one example of genetic mutation–based master protocol design clinical trials (see **Figure 9,** p. 57). These trials allow researchers to test one anticancer therapeutic on a group

THERAPEUTIC DEVELOPMENT

Target validation.
Potential 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 and robustly validate molecules that "hit" the target.

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

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

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

IND

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

Adapted from (1)

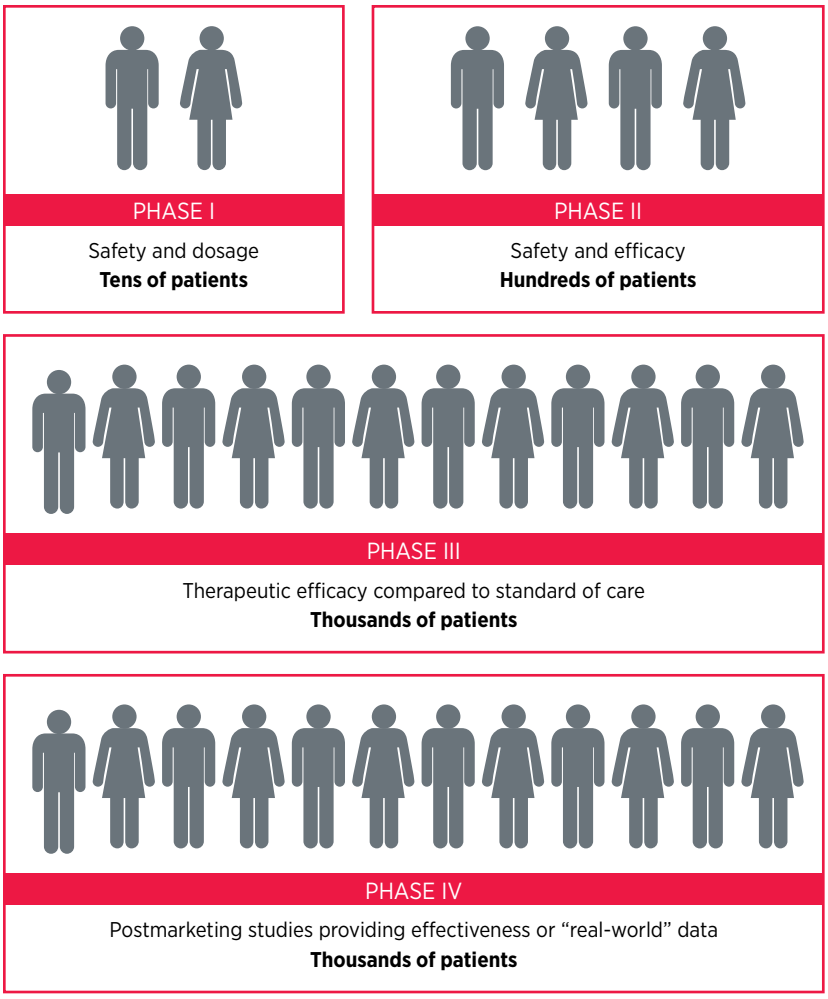
of patients who all have the same type of genetic mutation, regardless of the anatomic site of the original cancer. One new molecularly targeted therapeutic that was shown to work against an array of cancer types characterized by a specific genetic feature, or biomarker, in a number of basket trials is highlighted in **Targeting Cancers Based on Tumor Biomarker, Not Tumor Origin** (see p. 66) (166).

Two recent reports show that using biomarkers, such as the presence of a specific genetic mutation, does help to increase the efficiency of the clinical development of new therapeutics (162)(167). One report found that when considering all areas of medicine, candidate therapeutics entering phase I clinical trials that were matched to patients using biomarkers had a 25.9 percent chance of FDA approval, compared with 8.4 percent for candidates that were not matched using biomarkers (167). Another study looking at anticancer therapeutics estimated that the chance of FDA approval was 10.7 percent for candidate agents that were matched to patients using biomarkers, compared with 1.6 percent for unmatched candidates (162). These data indicate that we need to do more to improve the clinical trial enterprise.

Other pressing challenges that need to be overcome are low participation in clinical trials, in particular among adolescents and young adults, and a lack of diversity among those who do participate (168-171) (see sidebar on **Disparities in Cancer Clinical Trial Participation,** p. 54). Low participation in clinical trials means that some trials

FIGURE 8

PHASES OF CLINICAL TRIALS



Clinical trials evaluating potential new therapeutics for treating patients with cancer have traditionally been done in three successive phases, each with an increasing number of patients. Phase I studies are designed to determine the optimal dose of an investigational anticancer therapeutic, how humans process it, and potential toxicities. Phase II studies are designed to determine the initial efficacy of an investigational therapy, in addition to continually monitoring for potential toxicities. Phase III studies are large trials designed to determine therapeutic efficacy as compared to standard of care (placebos are rarely used in cancer clinical trials); when successful, the results of these trials can be used by the U.S. Food and Drug Administration (FDA) to approve new therapeutics or new indications for existing therapeutics. Phase IV studies are conducted after a therapy is provisionally approved by the FDA and provide additional effectiveness or "real-world" data on the therapy. Recent studies found that it takes about 13 years to complete phases I-III of clinical testing and regulatory assessment (161)(162). These studies also showed that the rate of success is low, with fewer than 10 percent of anticancer therapeutics that enter clinical trials ultimately obtaining FDA approval for use in cancer care.

Adapted from (36)

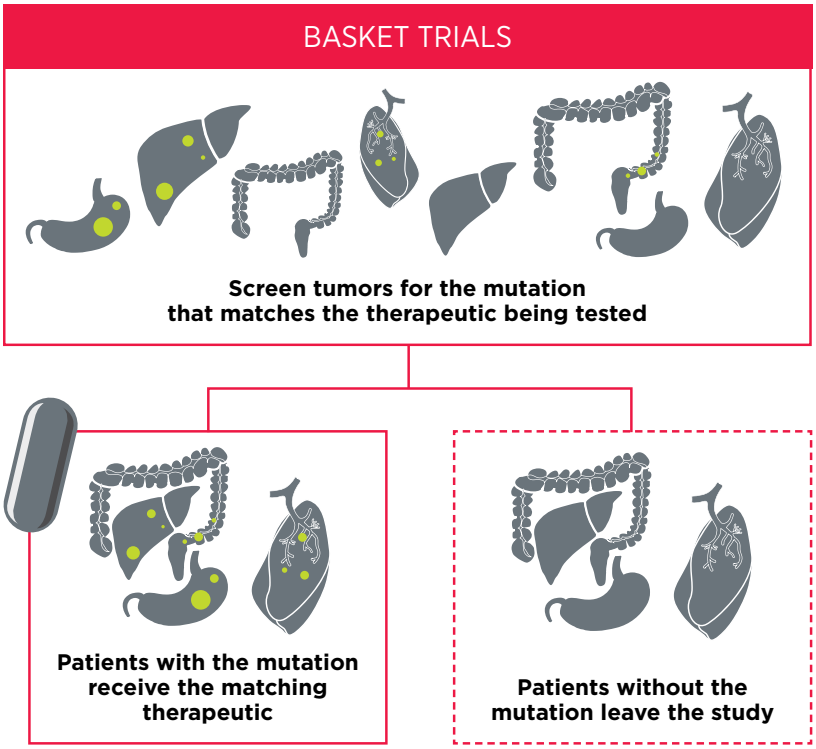
fail to enroll enough participants to draw valid conclusions about the effectiveness of the medical product being tested (172)(173). Understanding and then overcoming barriers to clinical trial participation for all segments of the population is vital if we are to accelerate the pace of progress against cancer for all.

PROGRESS ACROSS THE CLINICAL CANCER CARE CONTINUUM

Research discoveries made as a result of innovative cancer science are continually being translated to new medical products for cancer prevention, detection, diagnosis, treatment, and survivorship. The approval of new medical products is not the

FIGURE 9

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

Adapted from (109)

end of a linear research process. Rather, it is an integral part of the medical research cycle because observations made during the routine use of new medical products can be used to accelerate the pace at which similar products are developed and to stimulate the development of new, more effective products.

In addition, observations made during the real-world use of a product can be utilized to further enhance the use of that product. For example, the FDA utilized data from the real-world use of a molecularly targeted therapeutic called palbociclib (Ibrance) to approve the use of palbociclib as a treatment for men with advanced or metastatic breast cancer that tests positive for hormone receptor (HR) and negative for HER2 in April 2019. Given that there are only 2,670 men expected to be diagnosed with breast cancer in 2019 in the United States, conducting rigorous clinical trials of new treatments for these individuals is challenging. Thus, the use of real-world data to support FDA decision-making has accelerated the pace of progress for men with breast cancer such as **Kirby Lewis** (see p. 58).

The proportion of people with cancer who participate in a clinical trial varies by age. It is estimated that clinical trial participation is: about **60% among children younger than 15; <2% among adolescents and young adults (ages 15 to 39); and <5% among adults older than 39** (172).

"I HOPE THAT BY SHARING MY STORY I CAN SHOW OTHERS THAT LIFE DOESN'T END WHEN YOU GET A TERMINAL DIAGNOSIS, IT IS STILL WELL WORTH LIVING."

KIRBY LEWIS

AGE 58 | INWOOD, WEST VIRGINIA

RAISING AWARENESS OF MALE BREAST CANCER

It took a while for me to be diagnosed with breast cancer because the first doctor I saw after I felt a lump in my breast thought of it as a woman's disease. Once I transferred my care to the VA Hospital in Washington, DC, I received incredible care. I am currently taking fulvestrant (Faslodex) and palbociclib (Ibrance), which are keeping the metastatic tumor in my lung from progressing. This is a blessing because it is allowing me to continue living, continue working, and continue raising awareness of male breast cancer.

I was diagnosed with stage IIA breast cancer in April 2012, but it all started a few months earlier with a very persistent cough and symptoms of a cold. While in bed one night, I began coughing; as I sat up to get air, I grabbed my chest and felt a lump. I woke up my wife and said, "Honey, I've found a lump in my breast. I think I have breast cancer." Her response was, "If you have breast cancer, I have prostate cancer; now go to sleep."

Unfortunately, it turned out that I did have breast cancer, but it took a while to get the diagnosis. The first doctor I saw told me that "men don't get breast cancer," but then I went to a nearby VA Hospital in Washington, DC, because I am a veteran. After a series of tests, an open biopsy showed that I had ER-positive, PR-positive, HER2-negative breast cancer.

I had surgery to remove my left breast and several lymph nodes, which turned out to be free of cancer.

During the tests to prepare for the mastectomy, they discovered I needed open heart surgery because of several blocked arteries. Who knows what would have happened without those pretests, so I always say that "Breast cancer saved my life."

The open-heart surgery had to be delayed because the tamoxifen I was taking to reduce the chance that my breast cancer would recur or spread had driven my triglyceride levels up to what the doctors called industrial strength. So, I stopped taking tamoxifen and the 9½-hour open-heart surgery was a success.

Life was good for about four years, and then an X-ray showed tumors in my lungs in April 2016. Further scans and biopsies found additional tumors in my spine. The oncologist told me I had metastatic cancer. It was the hardest day of my life. It wasn't just the diagnosis; it was also the impact it had on my wife. She had always been so strong, but this devastated her.

I immediately began chemotherapy. There are no words to describe adequately how miserable, how tired, how pulled down your body gets while you are taking chemotherapy. After about three months, a scan showed that the tumors had shrunk a little but were still there.

My oncologist tried me on a number of different treatments over the next few months but most of them gave me severe side effects so I would have to stop taking them and switch to another.

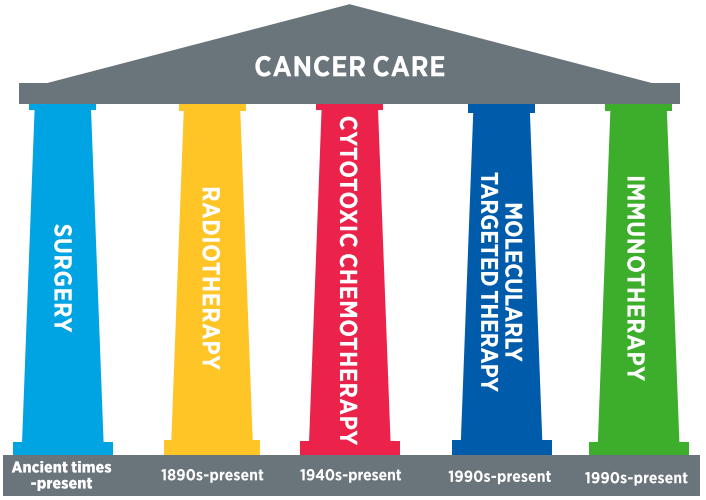
Amazingly, scans in November 2016 showed that there was no sign of the cancer in my body. I was over the moon. My oncologist attributed my new status of no evidence of disease to the treatments I had received; I like to think that prayer had something to do with it, too.

After that, I took fulvestrant and zoledronic acid (Zometa), which was to strengthen my bones, until a scan in August 2018 showed a small tumor in my right lung. Since January 2019, my oncologist has added palbociclib to the fulvestrant. I get fulvestrant injections once a month and I take palbociclib orally for 21 days, take nothing for 10 days, and then start the palbociclib again. This seems to be working because I'm not having severe side effects from the treatment and my most recent scans showed the tumor is stable and there are no signs of the cancer progressing. For someone with metastatic cancer, that is a blessing; after all, I'm still here and I hope that I'm doing something productive.

One of the things that I do now is raise awareness of male breast cancer. I am active in the advocacy community and I hope that by sharing my story I can show others that life doesn't end when you get a terminal diagnosis; it is still well worth living.

FIGURE 10

THE PILLARS OF CANCER CARE



Physicians often refer to the "pillars" of cancer treatment. For many years, there was only 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 original pillars—surgery, radiation, and cytotoxic chemotherapy—continue to be the standard of care for many patients. The first molecularly targeted therapeutics were introduced in the late 1990s, leading to the fourth pillar, molecularly targeted therapy. Likewise, the late 1990s laid the groundwork for the introduction of the fifth treatment pillar, immunotherapy. The number of anticancer therapeutics that form the most recent two pillars of cancer care continues to increase every year.

Adapted from (36)

New FDA-approved medical products are usually utilized alongside treatments already in use, including surgery, radiotherapy, and cytotoxic chemotherapy, which continue to be the mainstays of clinical cancer care (see **Figure 10, Supplemental Table 2,** p. 143, and **Supplemental Table 3,** p. 147).

The following discussion focuses primarily on the 17 new anticancer therapeutics approved by the FDA in the 12 months spanning this report, August 1, 2018 to July 31, 2019 (see **Table 5,** p. 61). Also highlighted are the 10 previously approved anticancer therapeutics that received FDA approval for treating additional types of cancer in that period. Not discussed are FDA approvals related to expanding the use of an anticancer therapeutic previously approved for a given type of cancer to include treatment with that therapeutic at different timepoints during the treatment of the same cancer type. For example, the May 2019 FDA approval expanded the use of the molecularly targeted therapeutic ado-trastuzumab emtansine (Kadcyla) to include postsurgery, or adjuvant, treatment of women with early-stage HER2-positive breast cancer (see **Figure 11,** p. 62). This expansion, which occurred more than 6 years after the molecularly targeted therapeutic was first approved for treating metastatic HER2-positive breast cancer, was based on results from a phase III clinical trial that showed that adjuvant ado-trastuzumab emtansine treatment reduced the risk of disease recurrence by half compared with standard treatment.

New medical products used across the continuum of clinical cancer care transform lives by improving survival and quality of life. However, not all patients receive the standard of care recommended for the type and stage of cancer that they have been diagnosed with (177-179) (see sidebar on **Disparities in Cancer Treatment,** p. 64). Thus, it is imperative that all stakeholders committed to driving progress against cancer work together to address the challenge of disparities in cancer treatment because these can be associated with adverse differences in survival. In fact, two recent studies showed that disparities in multiple myeloma and prostate cancer survival for African Americans compared with whites were eliminated if they had equivalent access to care and to standard treatments (180)(181).

TREATMENT WITH SURGERY

For many years, surgery was the only pillar of cancer treatment (see **Figure 10**). Today, it remains the foundation of curative treatment for many patients (184). One study found that patients diagnosed at the earliest stage, stage I, were more than five times as likely to be treated with surgery as patients diagnosed at the most advanced stage, stage IV

TABLE 5

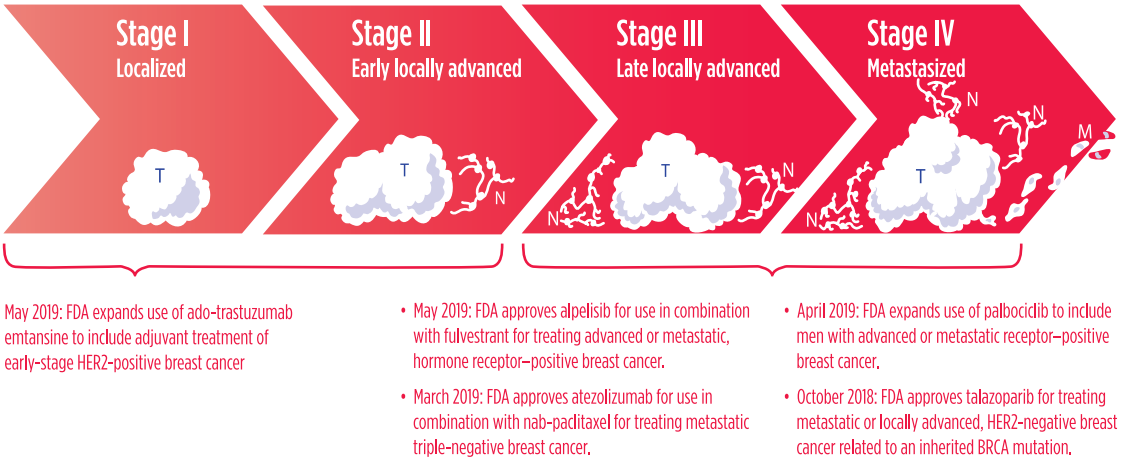
NEWLY FDA-APPROVED ANTICANCER THERAPEUTICS: AUGUST 1, 2018–JULY 31, 2019

APPROVED INDICATION	GENERIC NAME	TRADE NAME	
Angiogenesis Inhibitors			
Certain type of liver cancer†	cabozantinib	Cabometyx	
Certain type of liver cancer†	lenvatinib	Lenvima	
Certain type of liver cancer†	ramucirumab	Cyramza	
Antinutrients			
Certain type of leukemia	calaspargase pegol-mknl	Asparlas	
Cell-cytoskeleton Modifying Agents			
Certain type of non-Hodgkin lymphoma	polatuzumab vedotin-piiq	Polivy	
Cell-death Promoting Agent			
Certain type of leukemia†	venetoclax	Venclexta	
Cell-signaling Inhibitors			
Certain type of breast cancer	alpelisib*	Piqray	
Certain type of lung cancer	dacomitinib*	Vizimpro	
Certain types of leukemia and non-Hodgkin lymphoma	duvelisib	Copiktra	
Certain type of bladder cancer	erdafatinib*	Balversa	
Certain type of leukemia	glasdegib	Daurismo	
Certain type of leukemia	gilteritinib*	Xospata	
NTRK-positive solid tumors	larotrectinib	Vitrakvi	
Certain type of lung cancer	lorlatinib*	Lobrena	
Cell Lysis Mediators			
Certain types of non-Hodgkin lymphoma	mogamulizumab-kpkc	Poteligeo	
Certain type of leukemia	tagraxofusp-erzs	Elzonris	
DNA-damaging Agent			
Certain types of stomach cancer†	trifluridine AND tipiracil	Lonsurf	
DNA-repair Inhibitors			
Certain type of breast cancer	talazoparib*	Talzenna	
Hormones/Antihormones			
Prostate cancer	darolutamide	Nubeqa	
Immune-checkpoint Inhibitors			
Certain type of breast†* and lung† cancers	atezolizumab	Tecentriq	
Certain type of kidney cancer†	avelumab	Bavencio	
Certain type of skin cancer	cemiplimab-rwlc	Libtayo	
Certain type of lung cancer†	nivolumab	Opdivo	
Certain types of esophageal*†, kidney,† liver,† and lung† cancer, and Merkel cell carcinoma†	pembrolizumab	Keytruda	
Immune-system Modifier			
Certain types of non-Hodgkin lymphoma†	lenalidomide	Revlimid	
Immunotoxins			
Certain type of leukemia	moxetumomab pasudotox-tdfk	Lumoxiti	
Nuclear Export Inhibitors			
Multiple myeloma	selinexor	Xpovio	

†new cancer type approved 2018–2019
* requires a companion diagnostic

FIGURE 11

NEW FDA APPROVALS TARGET ALL STAGES OF BREAST CANCER



May 2019: FDA expands use of ado-trastuzumab emtansine to include adjuvant treatment of early-stage HER2-positive breast cancer

- May 2019: FDA approves alpelisib for use in combination with fulvestrant for treating advanced or metastatic, hormone receptor–positive breast cancer.
- March 2019: FDA approves atezolizumab for use in combination with nab-paclitaxel for treating metastatic triple-negative breast cancer.
- April 2019: FDA expands use of palbociclib to include men with advanced or metastatic receptor–positive breast cancer.
- October 2018: FDA approves talazoparib for treating metastatic or locally advanced, HER2-negative breast cancer related to an inherited BRCA mutation.

Clinical advances are benefiting patients diagnosed with breast cancer at both early and late stages of disease. During the 12 months covered by this report, August 1, 2018 to July 31, 2019, the U.S. Food and Drug Administration (FDA) approved two new therapeutics, alpelisib (Piqray) and talozaparib (Talzenna), and expanded the use of two previously approved therapeutics, atezolizumab (Tecentriq) and palbociclib (Ibrance), to treat patients with locally advanced or metastatic breast cancer. During the same period, the FDA also expanded the use of ado-trastuzumab emtansine (Kadcyla), previously approved to treat metastatic HER2-positive breast cancer, to include adjuvant treatment of early-stage HER2-positive breast cancer.

(185). Given the curative potential of surgery, these data highlight the important role of diagnosing cancer at the earliest possible stage.

Despite the immense benefits of surgery, complications are common and can negatively affect patient quality of life (186) (187). Enhanced recovery after surgery (ERAS) programs are emerging as one approach to address this issue. These multimodal, transdisciplinary programs focus on optimizing preoperative, intraoperative, and postoperative patient care using strategies that ensure the patient is as physically and emotionally fit for surgery as possible, alleviate the stress of surgery, promote recovery, and reduce the time before patients can begin adjuvant treatment. Providing patients with an individualized prehabilitation plan that includes exercise, nutrition, stress reduction, and smoking cessation components to optimize their physical fitness before surgery is one preoperative strategy included in some ERAS programs (188-190). The components of ERAS programs can vary depending on the type of surgery being performed and the center at which the surgery is being performed, but overall these programs have been successful. One study found that among patients undergoing surgery for lung cancer, the rate of postsurgery complications was significantly lower for those who participated in ERAS programs than it was for those who did not participate (187). Another showed that among patients undergoing surgery for colorectal cancer, those who participated in a prehabilitation plan that included exercise, protein supplementation, and relaxation were significantly more likely to rapidly regain their presurgery functional walking capacity than those who did not participate (189)(191).

Another approach to reducing the complications and improving quality of life after surgery is to perform less invasive surgery. Before such approaches to surgery can become standard of care, it is important that they are shown in rigorous, well-designed, large clinical trials to have no adverse effect on patient survival. The importance of such trials is highlighted by several recent studies showing that less invasive surgery may only benefit patients with certain types of cancer. One clinical trial showed that a less invasive form of surgery for esophageal cancer called hybrid minimally invasive esophagectomy resulted in fewer major complications during and after surgery than open

esophagectomy, and did not compromise disease-free and overall survival (192). In contrast, two other studies showed that minimally invasive surgery for early-stage cervical cancer is associated with shorter overall survival compared with open surgery (193)(194).

Reducing complications and improving quality of life after surgery can also be achieved by performing less extensive surgery. Two clinical trials recently found that surgical removal of large numbers of lymph nodes in the area around a cancer does not benefit all patients, and can be a source of surgical complications and long-term adverse effects (195)(196). In one trial, women who had early-stage breast cancer with defined clinical characteristics had equally good disease-free survival after 10 years whether or not they had an invasive surgical procedure called axillary lymph node dissection during or after breast cancer surgery. In the other trial, women with advanced ovarian cancer had equally good overall survival regardless of whether they had an invasive surgical procedure called a systematic pelvic and paraaortic lymphadenectomy as part of ovarian cancer surgery. In both trials, the women who did not have the additional surgical procedure had fewer complications after surgery.

TREATMENT WITH RADIOTHERAPY

Radiotherapy became the second pillar of cancer treatment in 1896 (see **Figure 10,** p. 60). Today, about 50 percent of patients receive radiotherapy to shrink or eliminate tumors or to prevent local recurrence (184) (see sidebar on **Using Radiation in Cancer Care,** p. 65).

Despite the immense benefits of radiotherapy, it can have long-term adverse effects that negatively impact patient quality of life. Stereotactic radiosurgery and stereotactic body radiotherapy are advanced approaches to radiotherapy that can more precisely target radiation to tumors than traditional radiotherapy. The high degree of precision means that higher doses of radiation can be used compared with traditional radiotherapy and that healthy tissues surrounding a tumor are spared from damage caused by the radiation, which can reduce the long-term adverse effects of radiotherapy. Given the potential benefits of stereotactic radiosurgery and stereotactic body radiotherapy there are many clinical trials testing ways to incorporate these treatments into clinical cancer care. For example, stereotactic radiosurgery 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 lead to equally good overall survival with less neurocognitive deterioration compared with whole brain radiotherapy (197).

Another recent advance in radiotherapy is the emergence of hypofractionated radiotherapy, whereby patients receive fewer but higher doses of radiotherapy compared with the traditional course of radiotherapy. Thus, patients who have hypofractionated radiotherapy complete their radiotherapy over a shorter period of time and in fewer treatment sessions. Hypofractionated radiotherapy is increasingly being used in the treatment of early-stage breast cancer and localized prostate cancer because it was recently shown to be as effective as traditional courses of radiotherapy at reducing cancer recurrence after 10 years (198)(199).

Typically, the only use of radiotherapy in the treatment of patients with metastatic cancer is to reduce or control symptoms of disease. However, several recent clinical trials have shown that radiotherapy targeted to the initial cancer from which tumors have metastasized can improve survival for patients who have metastatic tumors at a limited number of sites and are said to have oligometastatic disease. For example, two recent clinical trials have shown that adding prostate-targeted radiotherapy to standard treatment for metastatic prostate cancer significantly increased survival for patients who had limited metastatic disease (200)(201). Similar benefits have been seen for patients with lung cancer who have oligometastatic disease (202)(203).

TREATMENT WITH CYTOTOXIC CHEMOTHERAPY

Cytotoxic chemotherapy was the third type of treatment to become a pillar of cancer care (see **Figure 10,** p. 60). The use of this mainstay of cancer treatment is constantly evolving as researchers develop new cytotoxic chemotherapeutics and identify new ways to use existing cytotoxic chemotherapeutics to improve survival and quality of life for patients.

A New Therapeutic for Patients with Acute Lymphoblastic Leukemia

In December 2018, the FDA approved a new therapeutic called calaspargase pegol-mknl (Asparlas) for use as part of a multiagent cytotoxic chemotherapy regimen for children, adolescents, and young adults ages 1 month to 21 years who have acute lymphoblastic leukemia (ALL).

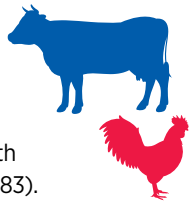
More than 50 percent of those diagnosed with ALL each year in the United States are children, adolescents, and young adults under the age of 22. Most are treated with a combination of four, or even five, chemotherapeutics. One of the chemotherapeutics in the most commonly used combination works by depleting the patient's body of a molecule called L-asparagine, which is one of the building blocks that cells use to create the proteins they need to function. ALL cells are unable to generate their own L-asparagine. Thus, depletion of this critical building block interferes with the ability of ALL cells to generate proteins and, ultimately, to survive.

DISPARITIES IN CANCER TREATMENT

Research is constantly powering the development of new cancer treatments. However, as a result of complex and interrelated factors (see sidebar **Why Do U.S. Cancer Health Disparities Exist? p. 15), several segments of the population have been found to be disproportionately less likely to receive standard recommended cancer treatments. Examples of these disparities include:**

Patients with intrahepatic cholangiocarcinoma who are black are 50 percent less likely to have surgery compared with patients who are white (182).

Women with ductal carcinoma in situ who live in rural areas are 29 percent less likely to receive radiotherapy after breast conserving surgery compared with women who live in urban areas (183).



Women with breast cancer who have an income <$100,000 were 44 percent less likely to receive presurgery, or neoadjuvant, chemotherapy compared with women who have an income >$100,000 (177).

Patients with multiple myeloma who are black are 21 percent less likely to receive the molecularly targeted therapeutic bortezomib (Velcade) compared with those who are white (178).

Patients with metastatic prostate cancer who are Hispanic are 50 percent less likely to be treated with the immunotherapeutic sipuleucel-T (Provenge) compared with those who are not Hispanic (179).

Chemotherapeutics that work by depleting L-asparagine are asparagine-specific enzymes. In many cases, the enzyme is linked to a molecule called polyethylene glycol forming a pegaspargase. This slows down clearance of the enzyme from the patient's body.

In calaspargase pegol-mknl, the linker used to attach the polyethylene glycol to the asparagine-specific enzyme is different from the linkers used in other pegaspargase chemotherapeutics. The new linker is even more stable than previous linkers, which further slows down clearance of the enzyme from a patient's body (204). Thus, patients can go longer between doses of calaspargase pegol-mknl than they can between doses of other pegaspargase chemotherapeutics.

Treating Stomach Cancer in a New Way

In February 2019, the FDA approved a new use for Lonsurf, which is a single tablet that contains a combination of the cytotoxic chemotherapeutic trifluridine and a drug called tipiracil. The trifluridine–tipiracil combination tablet was approved for treating certain patients with stomach cancer, which is sometimes called gastric cancer, or gastroesophageal junction adenocarcinoma, which is cancer of the part of the esophagus that connects to the stomach. It was first approved by the FDA for treating advanced colorectal cancer in September 2015.

Trifluridine and tipiracil work together against cancer. Trifluridine causes damage to DNA in the rapidly multiplying cancer cells, which can ultimately trigger cell death; tipiracil prevents rapid breakdown of trifluridine, thereby maintaining adequate levels of the cytotoxic chemotherapeutic in the body.

Trifluridine damages DNA in a similar way to other cytotoxic chemotherapeutics called fluoropyrimidines, which have been used as a treatment for stomach cancer for decades. In a phase III clinical trial, the trifluridine–tipiracil combination tablet improved survival compared with placebo even for those patients who had stomach cancer or gastroesophageal junction adenocarcinoma that was no longer responding to treatment with fluoropyrimidine-containing chemotherapy regimens (205). On the basis of these results, the FDA approved Lonsurf for treating adult patients with metastatic stomach cancer or gastroesophageal junction adenocarcinoma that has progressed despite treatment with at least two other cytotoxic chemotherapy regimens, including one that includes a fluoropyrimidine.

Tailoring Cytotoxic Chemotherapy: Less Is Sometimes More

Treatment with cytotoxic chemotherapeutics can have adverse effects on patients. These effects can occur during treatment and continue long-term or they can appear months or even years later. As a result, health care providers

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 shrink a cancer so that it can be subsequently treated by a different method such as surgery.

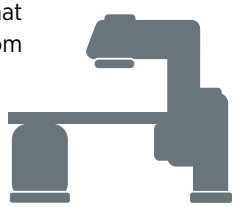
Adjuvant radiotherapy seeks to eliminate any remaining cancer following prior treatment.

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

Types of Radiotherapy

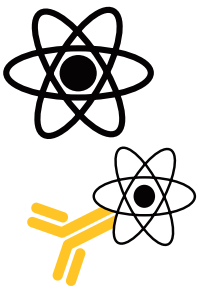
Particle therapy uses protons or carbon ions rather than X-rays as the source of energy. In contrast to X-rays that pass though the body, losing energy and causing damage to the noncancerous tissues through which they pass, these heavier particles deposit most of their energy in the target. In this manner,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

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.



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

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



Adapted from (36)

and researchers are investigating whether less aggressive chemotherapy regimens can allow some patients the chance of an improved quality of life without an adverse effect on their survival.

In one recent phase III clinical trial involving frail or elderly patients with advanced stomach or esophageal cancer, researchers investigated how to optimize treatment with a combination of the cytotoxic chemotherapeutics oxaliplatin and capecitabine to be as effective as possible at slowing progression of the cancer while allowing the patients to maintain quality of life (206). They found that the lowest dose of oxaliplatin and capecitabine, which was 60 percent of the highest dose, was comparable to the highest dose in terms of delaying disease progression, but that it caused fewer adverse side effects and allowed patients to maintain a higher quality of life.

Another group for whom treatment de-escalation might be possible is patients with breast cancer who have an excellent response to chemotherapy given before surgery (neoadjuvant chemotherapy) (207). In a recent study, researchers found that patients who had no signs of invasive cancer in the breast tissue and lymph nodes removed during surgery following neoadjuvant chemotherapy (that is, patients who had a pathologic complete response) were less likely to have disease recurrence and were more likely to survive than those patients who did not have a pathologic complete response. The link between having a pathologic complete response after neoadjuvant chemotherapy and improved outcomes was seen regardless of whether the patient had additional chemotherapy after surgery. As this study was not a randomized clinical trial, further clinical trials are needed before this approach to treatment de-escalation can be considered for implementation in the clinic.

A third group for whom it might be appropriate to use less cytotoxic chemotherapy than is currently recommended is children with a rare type of liver cancer, called hepatoblastoma, who have had surgery to remove the tumor (208). About 100 children are newly diagnosed with hepatoblastoma each year in the United States. Among these children, about one-third have tumors that can be surgically removed as the initial treatment after diagnosis. Surgery has traditionally been followed by four cycles of a chemotherapy regimen comprising three cytotoxic chemotherapeutics—cisplatin, fluorouracil, and vincristine. Surgery followed by cytotoxic chemotherapy yields good outcomes for patients, with about 90 percent surviving 5 or more years after diagnosis. However, cytotoxic chemotherapy causes many adverse effects. In a recent small phase III clinical trial, 91 percent of patients with hepatoblastoma who had surgery at diagnosis and were then treated with two rather than four cycles of cisplatin, fluorouracil, and vincristine were alive 5 or more years after diagnosis (208). Thus, reducing postoperative chemotherapy might provide a way to reduce the risk of acute and long-term side effects from cytotoxic chemotherapy for certain patients with hepatoblastoma without an adverse effect on their survival. Results from another clinical trial suggest that it might be possible to postoperatively treat patients with hepatoblastoma with only cisplatin and then treat them with sodium thiosulfate to reduce their risk of hearing loss, which is one of the common adverse effects of cisplatin (209). Larger clinical trials are underway to confirm these data.

TREATMENT WITH MOLECULARLY TARGETED THERAPY

Remarkable advances in our understanding of the biology of cancer, including the identification of numerous genetic mutations that fuel tumor growth in certain patients, set the stage for the new era of precision medicine, an era in which the standard of care for many patients is changing from a one-size-fits-all approach to one in which greater understanding of the individual patient and the characteristics of his or her cancer dictates the best treatment option for the patient (see **Understanding How Cancer Develops,** p. 17).

Therapeutics directed to the molecules influencing cancer cell multiplication and survival target the cells within a tumor more precisely than cytotoxic chemotherapeutics, which target all rapidly dividing cells, thereby limiting damage to healthy tissues. The greater precision of these molecularly targeted therapeutics tends to make them more effective and less toxic than cytotoxic chemotherapeutics. As a result, they are not only saving the lives of patients with cancer, but also allowing these individuals to have a higher quality of life.

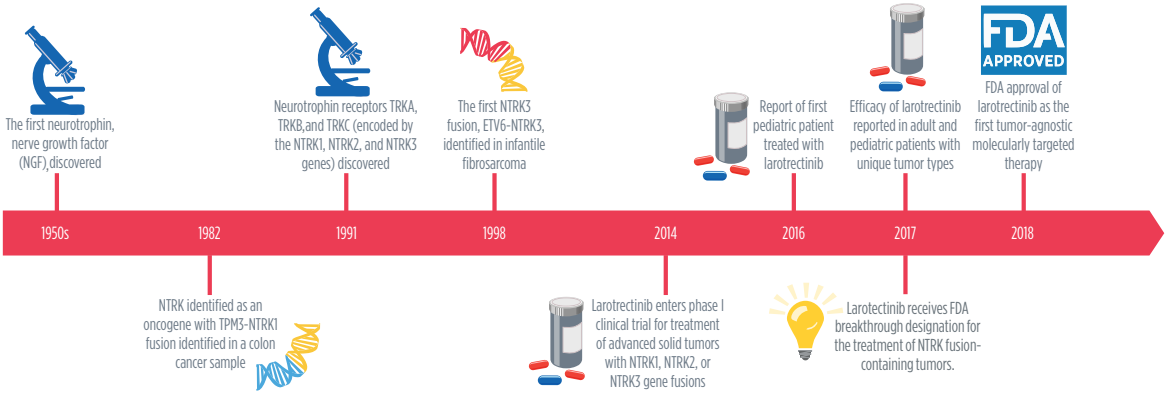
In the 12 months spanning August 1, 2018 to July 31, 2019, the FDA approved 14 new molecularly targeted anticancer therapeutics (see **Table 5,** p. 61). During this period, they also approved four previously approved molecularly targeted anticancer therapeutics for treating additional types of cancer.

Targeting Cancers Based on Tumor Biomarker, Not Tumor Origin

One of the most significant precision medicine advances in the 12 months spanning this report was the first FDA approval of a molecularly targeted therapeutic to treat cancer based on the presence of a specific genetic biomarker in the tumor irrespective of the site at which the tumor originated. The therapeutic, larotrectinib (Vitrakvi), was approved by the FDA in November 2018 for treating children and adults who have solid tumors that test positive for the NTRK gene fusion biomarker.

FIGURE 12

RESEARCH MILESTONES ON THE ROAD TO DEVELOPING LAROTRECTINIB



Larotrectinib (Vitrakvi) is the first molecularly targeted therapeutic to be approved by the FDA for use in a tissue-agnostic way. Since its November 2018 approval, larotrectinib has been benefiting children and adults who have solid tumors that test positive for the NTRK gene-fusion biomarker. Decades of basic, translational, and clinical research paved the way for the landmark approval of larotrectinib, starting with the seminal identification of the first neurotrophin, nerve growth factor, in the 1950s. Other basic research milestones on the way to the FDA approval are the identification of the neurotrophin receptor proteins, TRKA, TRKB, and TRKC, and the genes that encode these proteins, NTRK1, NTRK2, and NTRK3, and the discovery that NTRK fusion genes and proteins fuel the growth of a wide array of cancer types that occur in adults and children. Together, this body of research led to the development of larotrectinib, which targets TRKA, TRKB, and TRKC, and its testing in basket clinical trials involving patients who have cancers driven by an NTRK gene fusion.

The approval of larotrectinib for use in a tissue-agnostic way followed several decades of basic, translational, and clinical research (see **Figure 12**).

Larotrectinib targets three related proteins called TRKA, TRKB, and TRKC. The genes NTRK1, NTRK2, and NTRK3 provide the code that cells use to make these proteins.

Structural changes in chromosomes that involve the three NTRK genes and lead to the production of NTRK gene fusions, and subsequently to TRK fusion proteins, have been identified in a diverse array of cancer types that occur in adults and children (166) (see sidebar on **Genetic Mutations,** p. 20). These include many rare types of cancer, including mammary analogue secretory carcinoma of the salivary gland, infantile fibrosarcoma, and cholangiocarcinoma. Overall, researchers estimate that NTRK gene fusions fuel the growth of up to 1 percent of all solid tumors.

Larotrectinib was approved after it was shown in three basket trials (see **Figure 9** p. 57) that 75 percent of patients treated with the molecularly targeted therapeutic had complete or partial tumor shrinkage (166). There were 17 types of cancer represented among the group of 55 patients enrolled in the three trials, with the most common being mammary analogue secretory carcinoma of the salivary gland. Tumor shrinkage was seen across cancer types. Thus, the approval provides a new treatment option and new hope to patients with a wide range of types of cancer, including children with soft tissue sarcoma, such as **Emma Levine** (see p. 68), and adults with salivary gland tumors, such as **Keith Taggart** (see p. 70).

"IT (LAROTRECTINIB) HAS BEEN A MIRACLE DRUG FOR HER. AS OF JULY 31, 2019 HER CANCER IS ALMOST UNDETECTABLE."

EMMA LEVINE

AGE 14 | PLEASANT VALLEY, NEW YORK

FIGHTING CHILDHOOD CANCER WITH LAROTRECTINIB

A MESSAGE FROM JENNIFER HUBER AND KEVIN LEVINE, EMMA'S PARENTS

Our daughter Emma was diagnosed with undifferentiated soft tissue sarcoma in August 2016. By March 2018, we were preparing for the worst because chemotherapy was not keeping the cancer at bay. Then, on June 22, 2018, we got the call of a lifetime; genetic profiling of Emma's tumor had revealed she was a candidate for a clinical trial testing a promising new treatment called larotrectinib (Vitrakvi). Within days, we had enrolled Emma in the clinical trial, and she began taking larotrectinib. It has been a miracle drug for her. As of July 31, 2019 her cancer is almost undetectable, and she is living the life of a typical teenager.

Emma's diagnosis came in the summer after she finished fifth grade. She had been having abdominal pain, losing weight, and her Tourette syndrome symptoms had been intensifying for a few months, but none of the doctors we saw could figure out what was wrong.

At yet another visit to her pediatrician, Emma had an ultrasound. It revealed a 10-centimeter tumor on her right kidney. We went straight to the local children's hospital, where a CT scan confirmed the devastating news: Emma had cancer. She was immediately admitted to the pediatric oncology ward, and our lives were forever changed.

Within days Emma had surgery. Because the tumor was intertwined with her kidney, her entire right kidney was removed along with the tumor.

Emma spent the rest of August in the hospital recovering from the surgery. During that time, we had an agonizing wait to find out exactly what type of cancer it was and what Emma's treatment would be moving forward.

It turned out that the cancer was an undifferentiated soft tissue sarcoma and only in her kidney. Emma began the first of seven cycles of chemotherapy the day she was supposed to start middle school. This treatment, which Emma received alongside 26 doses of radiation to the abdomen, was brutal. Emma spent much of the next 5 months in the hospital. But at the end of it, the scans showed no evidence of cancer. She was in remission. We thought the worst was behind us and began to resume life.

Then, in November 2017, Emma's routine check-up scan showed that the cancer had returned and this time was in Emma's lungs. We were utterly devastated. She had stage IV cancer and the prognosis was grim.

We were advised to enjoy Christmas with Emma and then start chemotherapy in the New Year, which we did. She only managed three cycles of the chemotherapy, however, because the side effects were unbearable, and the treatment was not keeping the cancer at bay.

At this point, Emma was in emotional turmoil and we transitioned to palliative chemotherapy. This allowed Emma to be treated at home and improved her quality of life a little.

While we were meeting to discuss hospice intake, we never gave up hope. That is why we followed our local oncologist's recommendation to have Emma's tumor genetically profiled by researchers at Dana-Farber/Boston Children's.

Several months later, our local oncologist called to tell us to go straight to Boston. The genetic profiling had shown that Emma's cancer was driven by an NTRK fusion. This meant she was a candidate for a clinical trial testing an investigational treatment [larotrectinib] that was showing a lot of success against cancers caused by NTRK fusions.

Within a month of starting larotrectinib, Emma's health began improving and her 1-month scans showed the tumors had shrunk by 50 percent. A month later, the tumors had shrunk even further.

The difference in Emma's quality of life while taking larotrectinib and while taking chemotherapy is like night and day. Chemotherapy left Emma emaciated and weak. She could not go to school and was frequently in the hospital. Since starting larotrectinib, Emma has gained almost 30 pounds and she just enjoyed her eighth-grade dance after completing her first full year of middle school.

Emma will continue to take larotrectinib and to have regular check-up scans for many years, if not the remainder of her life.

Larotrectinib saved Emma's life, and we are so grateful to our local oncologist and everyone at Dana-Farber/Boston Children's, especially Dr. Janeway and Dr. DuBois. It has been a true collaboration, and we are very blessed to have such caring and dedicated people fighting in Emma's corner with us.

"...LAROTRECTINIB (VITRAKVI), HAS BEEN AMAZINGLY EFFECTIVE."

KEITH TAGGART

AGE 63 | OKLAHOMA CITY, OKLAHOMA

ANTICIPATING A LONG, HEALTHY LIFE THANKS TO LAROTRECTINIB

Two years after being diagnosed with salivary gland cancer, I was told surgery could no longer keep the cancer at bay because it had spread throughout my body. I was offered a choice between chemotherapy, which might get me three or four more weeks of life, or a clinical trial testing a new targeted treatment. I chose the clinical trial. The treatment, larotrectinib (Vitrakvi), has been amazingly effective. My cancer has been undetectable for about 2 years, and I am planning on living a long, healthy life.

I was diagnosed with salivary gland cancer in October 2014. I had noticed a lump about the size of a pea in my cheek and my primary care physician had referred me to an oral surgeon to have it removed. Although the oral surgeon thought there was no cause for worry at the time, a week later he called me back to his office and told me tests showed the lump was cancer. I was shocked and all I could hear during the conversation was "cancer." It was only on the drive home that it started hitting me and I realized that I had questions. What would happen next? What treatments did I need? What would my future look like?

An appointment with a surgeon here in Oklahoma City reassured me. He recommended removing a wider margin of tissue around the spot where the tumor had been, followed by seven weeks of radiation. I thought, great, I'll be fine once the surgery is done because all the cancer will be removed.

It didn't work out like that. Before I finished the radiation, I noticed more lumps in my cheek.

I had more surgery to remove those tumors. But not long after, lumps appeared in my other cheek. Over the course of a year, I had four surgeries.

At this point, I turned to The University of Texas MD Anderson Cancer Center for treatment. Because I already had new tumors, they scheduled me for more surgery and another seven weeks of radiation.

Again, this did not control the cancer. As soon as I recovered from one surgery, more tumors would appear. In December 2016, after my most extensive surgery, I went on a cruise with my family to celebrate the holidays. Even though I was very sick by this point—I had lost a lot of weight, I was constantly lethargic and tired, and I had many aches and pains—I still didn't realize the gravity of my situation.

After the cruise, things changed quickly. My surgeon told me the cancer was growing too fast for him to keep up and he was worried it might have spread to other parts of my body. CT scans revealed tumors in my lungs, liver, and kidney. I was devastated. Then, just two hours after learning "I was totally eat up with cancer," as we say in Oklahoma, a medical oncologist told me that chemotherapy could get me three or four more weeks of life. It was the first time I had realized I might die and I started spiraling downward mentally and emotionally.

Fortunately, the medical oncologist had also noticed in my medical records that genomic testing of my tumor had revealed an NTRK gene fusion and she recalled receiving emails about a clinical trial underway at MD Anderson that was recruiting patients with cancers with these gene fusions. I jumped at the chance to participate. Within hours I had spoken to the clinical trial administrator and begun the process of enrolling.

After taking a single larotrectinib pill twice a day for just four days, the tumors in my neck, face, and chest had shrunk so much I could no longer feel them. After four weeks, CT scans showed that all except one of my tumors had gone. The one left had shrunk by 65 percent. Over time, it continued to shrink, and it has been undetectable for about 2 years.

I will keep taking larotrectinib as long as it keeps my cancer away. Right now, the quality of my life is extraordinary. I go to the gym and run two miles on the treadmill every day, and I haven't missed a day's work due to cancer-related illness since I started the clinical trial.

One of the reasons I choose to talk about my experience is that I want to spread the word about this wonderful drug and how genomic testing of my tumor played a vital role in getting me into the clinical trial that saved my life.

Providing New Options for Patients with Breast Cancer

Despite major advances in the treatment of breast cancer, this disease is the second-leading cause of cancer-related death for women in the United States (2). Recent FDA decisions have the potential to power more progress against breast cancer because they have provided new molecularly targeted therapeutic treatment options for certain patients with the disease.

For patients with breast cancer, one factor determining what treatment options should be considered is the presence or absence of three tumor biomarkers, two hormone receptors and HER2. About 70 percent of breast cancers diagnosed in the United States are characterized as hormone receptor–positive and HER2-negative (210). Potential treatment options for these patients include therapeutics such as tamoxifen, which works by preventing the hormone estrogen from attaching to its receptor; letrozole, which works by lowering the level of estrogen in the body; and fulvestrant, which works by reducing the number of receptors for estrogen to bind to and by preventing estrogen from attaching to its receptor. 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**). In May 2019, the FDA approved the molecularly targeted therapeutic alpelisib (Piqray) as a new treatment option to help address this challenge.

Alpelisib works by blocking the function of phosphatidylinositol 3-kinase (PI3K) alpha, which has an important role in driving cell multiplication and survival. Research has shown that mutations in the PIK3CA gene, which provides the code that cells use to make the PI3K-alpha protein, promote the multiplication and survival of about 40 percent of hormone receptor–positive, HER2-negative breast cancers (211).

Alpelisib was approved by the FDA for use in combination with fulvestrant for treating men and postmenopausal women who have advanced or metastatic, hormone receptor–positive, HER2-negative breast cancer that tests positive for PIK3CA mutations and has progressed during or after endocrine therapy. This approval was based on results from a phase III clinical trial that showed that adding alpelisib to fulvestrant almost doubled the time before disease progression (211).

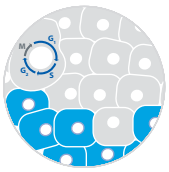
At the same time that the FDA made the decision about alpelisib, it approved the therascreen PIK3CA RGQ PCR Kit as a companion diagnostic to test patients for PIK3CA mutations (see sidebar on **Companion Diagnostics,** p. 73). This companion diagnostic can be used to test either tumor tissue or circulating tumor DNA isolated from blood samples, which can reduce the invasiveness of testing (see **Liquid Biopsies,** p. 108).

Another FDA decision that provided an advance against breast cancer was the October 2018 approval of the molecularly targeted therapeutic talazoparib (Talzenna) for treating patients with metastatic or locally advanced, HER2-negative breast cancer who have inherited a known or suspected cancer-associated BRCA1 or BRCA2 mutation. At the same time, the FDA approved using the BRACAnalysis CDx test as a companion diagnostic to identify patients who are eligible for talazoparib.

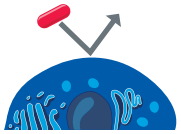
THE CHALLENGE OF TREATMENT RESISTANCE

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

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

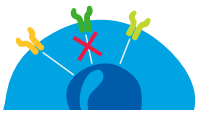


Some cancer cells in a tumor may have or may acquire mutations in the target of a given treatment that render the treatment ineffective.

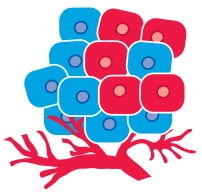


Some cancer cells in a tumor may have or may acquire molecular or cellular differences other than changes in the treatment target that render the treatment ineffective.

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



Differences in tumor microenvironment components can render a treatment ineffective.



Adapted from (1)

About 5 percent of all breast cancers diagnosed in the United States are attributable to an inherited BRCA1 or BRCA2 mutation (210).

The reason that the presence of a BRCA1 or BRCA2 mutation is relevant relates to the way that talazoparib works. Talazoparib 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. 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.

The approval of talazoparib was based on results from a phase III clinical trial that showed that treatment with the molecularly targeted therapeutic significantly increased the time to disease progression compared with treatment with a cytotoxic chemotherapeutic (212).

Given the benefits of talazoparib and another PARP inhibitor called olaparib (Lynparza) for patients with metastatic or locally advanced, HER2-negative breast cancer who have inherited a known or suspected cancer-associated BRCA1 or BRCA2 mutation, patients should talk with their health care providers about whether they are at high risk for having inherited one of these mutations and whether genetic testing is right for them. This is important because a recent study found that half of patients with breast cancer who were at high risk for having inherited a known or suspected cancer-associated BRCA1 or BRCA2 mutation had not had a genetic test (213).

Treating Bladder Cancer with a Novel Therapeutic

Bladder cancer is the sixth most commonly diagnosed cancer in the United States, with more than 80,000 new cases expected to be diagnosed in 2019 (2).

More than 90 percent of bladder cancers diagnosed in the United States are classified as urothelial carcinomas because they arise in cells that comprise the transitional cell urothelium that lines the bladder. Research has shown that up to 30 percent of urothelial carcinomas have a mutation in one of the four FGFR genes, with the most common being mutations in the FGFR3 gene (214). These mutations help promote the multiplication and survival of the cells within the urothelial carcinoma.

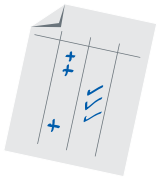
Erdafitinib (Balversa) targets FGFR proteins. In April 2019, it was approved for treating patients who have locally advanced or metastatic urothelial carcinoma that tests positive for FGFR2 or FGFR3 genetic mutations and that has progressed during or after treatment with a platinum-based cytotoxic chemotherapeutic. The approval was granted after it was shown in a phase II clinical trial that more than one-third of the patients who received erdafitinib had complete or partial tumor shrinkage.

At the same time that the FDA made the decision about erdafitinib, it approved the therascreen FGFR RGQ RT-PCR Kit as a companion diagnostic to identify patients with urothelial carcinoma who are eligible for the molecularly targeted therapeutic, such as **Gary Price** (see p. 74).

COMPANION DIAGNOSTICS

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

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



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

- accurately match patients with a specific therapy;

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

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

Adapted from (1)


"ERDAFITINIB HAS STOPPED THE TUMOR
FROM GROWING FOR THREE YEARS NOW,
AND ... I AM MAKING THE BEST OF MY LIFE.

GARY PRICE

AGE 59 | WILLIS, TEXAS

LIVING THE BEST LIFE POSSIBLE WITH METASTATIC BLADDER CANCER

Almost three years after I was first diagnosed with bladder cancer, I learned that it had metastasized. Aggressive chemotherapy did not stop the cancer, and I was told I had just months to live. But then I took part in a clinical trial testing a new medicine, erdafitinib (Balversa). Erdafitinib has stopped the tumor from growing for three years now, and although I have some serious side effects from the medicine, I am making the best of my life.

It all started in the summer of 2013, when I noticed some blood in my urine. The first time it happened was startling, but I didn't worry too much. Then it happened again and again, so I went to my primary care physician who recommended a series of tests. An ultrasound showed that my right kidney was extremely enlarged, which led to an MRI that showed a mass in my bladder. Finally, my local urologist did a cystoscopy, and I was told that I had bladder cancer.

It was very traumatic to hear the words, "you have cancer." I immediately wondered if it was a death sentence, but the urologist reassured me that the cancer had not spread out of the bladder and that they could treat it.

Days after the diagnosis, I had surgery to remove the tumor. It was as big as a billiard ball and blocking the tube from my right kidney to my bladder, which is why the kidney was so enlarged.

After the surgery, I had several treatments with BCG, but they did not keep me free of cancer. Over the next year or so, I had surgery five or six times to remove papillary-type tumors that kept growing in my bladder. My oncologist told me that these were not as aggressive as the first tumor that was removed but he recommended that I transfer my treatment to The University of Texas MD Anderson Cancer Center.

The medical team there recommended more extensive surgery, and in June 2015 I had a 15-hour surgery to remove my bladder, my right kidney, which had been so badly damaged that it was no longer functioning, my right ureter [the tube connecting the kidney and bladder], and my prostate.

The surgery was life changing. For example, I have an ostomy bag that I deal with every day, but it was something that I had to do to give myself the best chance of beating the cancer.

I was cancer free for just under a year. In April 2016, my routine follow-up scans showed a nodule in a scar that I had from where a drain from my kidney had been placed. A biopsy showed that it was the bladder cancer. I had metastatic disease.

I spent three days in the hospital receiving a very aggressive chemotherapy treatment, but that didn't stop the tumor from growing. I needed something different.

The oncologist checked a sample of my tumor and told me it had an alteration in a certain receptor, the FGFR3 receptor. She also said that she was involved in a clinical trial testing a new medicine for people with cancer that has an alteration in this receptor. I felt that it was my best choice and I have been taking erdafitinib ever since.

I am not cancer free, but the erdafitinib has controlled the growth of the tumor. It remains the size of a pea.

The erdafitinib does not make me sick like standard chemotherapy does for many people, but I have had to learn to live with some serious side effects. I have hand-foot syndrome, which means my hands and feet hurt severely all the time and it is hard to use my hands, so I can't open pop tops on cans or play the guitar anymore. I also can't taste salt and the nails on my fingers and toes lift off.

I don't dwell on the negatives; I continue to live my life as well as I can. I go to work every day, my wife and I started a new business, and I schedule competing in clay pigeon shooting tournaments months in advance.

Before my diagnosis, I had barely even heard of bladder cancer, but it is the sixth most common cancer diagnosed in the United States. I hope that by sharing my experience I can increase awareness about bladder cancer and the need for research funding.

Adding Precision to the Treatment of Blood Cancers

Cancers that arise in blood-forming tissues, such as the bone marrow, or in cells of the immune system are called blood cancers, or hematologic cancers. In the 12 months covered by this report, the FDA has made numerous decisions that are transforming the lives of patients with a wide array of hematologic cancers, including approving seven new molecularly targeted therapeutics for patients with some of these diseases (see sidebar on **Recent Advances against Blood Cancers,** p. 77).

Acute myeloid leukemia (AML) is the most commonly diagnosed type of leukemia in the United States, with 21,450 new cases anticipated in 2019 (2). It is also the type of leukemia with the lowest overall 5-year relative survival rate, 28 percent (8). In November 2018, the FDA made three decisions that provided new treatment options for defined groups of patients with this devastating disease.

One of these decisions was the approval of gilteritinib (Xospata), which targets FLT3. Mutations in the FLT3 gene promote the multiplication and survival of AML cells in 25 percent to 30 percent of cases, and patients with this type of AML have particularly poor outcomes (215). Gilteritinib was approved for treating adults who have AML that tests positive for a FLT3 mutation and that has not responded to or has relapsed after initial treatment. The approval was based on early results from a phase III clinical trial that showed that 21 percent of patients who received gilteritinib had complete remission (this means they had no evidence of disease and full recovery of blood counts) or complete remission with partial hematologic recovery (meaning no evidence of disease and partial recovery of blood counts). Subsequent results from the trial showed that gilteritinib also almost doubled median overall survival compared with standard chemotherapy regimens (216).

At the same time that the FDA made the decision about gilteritinib, it approved expanding the use of the LeukoStrat CDx FLT3 Mutation Assay to allow it to be used as a companion diagnostic to identify patients with FLT3 mutation–positive AML who are eligible for treatment with the new molecularly targeted therapeutic.

The FDA approved a second new molecularly targeted therapeutic for the treatment of AML in November 2018, glasdegib (Daurismo). Glasdegib targets a protein called Smoothened, which is part of a signaling pathway implicated in driving AML progression (217). Glasdegib was approved for use in combination with a low dose of the cytotoxic chemotherapeutic cytarabine for treating patients newly diagnosed with AML who are 75 or older or who have other chronic health conditions or diseases (comorbidities) that prevent them from having standard intensive cytotoxic chemotherapy. The approval was based on results from a phase II clinical trial that showed that adding glasdegib to low-dose cytarabine almost doubled median overall survival (218).

In November 2018, the FDA also approved expanding the use of the molecularly targeted therapeutic venetoclax (Venclexta) to include the treatment of patients newly diagnosed with AML who are 75 or older or who have comorbidities that prevent them from having standard intensive cytotoxic chemotherapy. Venetoclax targets the protein BCL-2, which promotes cell survival by preventing cells from undergoing a natural self-destruct process called apoptosis. Research has shown that levels of BCL-2 are frequently elevated in several types of leukemia cells, including AML cells and chronic lymphocytic leukemia (CLL) cells, and that it promotes the survival of these cells (219). By blocking BCL-2, venetoclax triggers the leukemia cells to die by apoptosis.

The approval of venetoclax for treating AML is for use of the molecularly targeted therapeutic in combination with any one of the cytotoxic chemotherapeutics azacitidine, decitabine, or low-dose cytarabine. It was based on results from two phase I/II clinical trials. In one of the trials, 67 percent of patients who received venetoclax and azacitidine had complete remission and 54 percent of patients who received venetoclax and decitabine had complete remission (219). In the other trial, 21 percent of patients who received venetoclax and low-dose cytarabine had complete remission. Venetoclax was first approved by the FDA for treating certain patients with CLL in April 2016.

CLL arises in immune cells called B cells, as do several other types of blood cancer, including small lymphocytic lymphoma (SLL). CLL and SLL are essentially the same disease, but have different names depending on where in the body the cancer cells accumulate. CLL cells are found mostly in the blood and bone marrow, whereas SLL cells are found mostly in the lymph nodes. In September 2018, the FDA approved a new molecularly targeted therapeutic for treating patients with CLL/SLL, duvelisib (Copiktra). Duvelisib targets PI3K-delta and PI3K-gamma, which are protein components of signaling pathways that have a key role in promoting the survival and expansion of CLL/SLL cells (220). Duvelisib was approved by the FDA for treating patients with CLL/SLL whose disease has progressed after they have received at least two other types of treatment. The approval was based on results from a phase III clinical trial that showed that a significantly greater proportion of patients responded to treatment with duvelisib compared with the standard treatment, ofatumumab (Arzerra) (220). The median time to disease progression was also longer among those who received duvelisib.

RECENT ADVANCES AGAINST BLOOD CANCERS

In the 12 months from August 1, 2018 to July 31, 2019, the U.S. Food and Drug Administration made numerous decisions that are transforming the lives of patients with a wide array of hematologic cancers, including the following:

Acute Lymphoblastic Leukemia (ALL) in Adults

- Calaspargase pegol-mknl (Asparlas) is a chemotherapeutic approved in December 2018 for use as part of a multiagent cytotoxic chemotherapy regimen for children, adolescents, and young adults ages 1 month to 21 years.
- ClonoSEQ assay is a next-generation sequencing–based test approved in September 2018 for determining whether a patient has minimal residual disease, or very low levels of cancer cells remaining, after treatment.

Acute Myeloid Leukemia

- Glasdegib (Daurismo) is a molecularly targeted therapeutic approved in November 2018.
- Gilteritinib (Xospata) is a molecularly targeted therapeutic approved in November 2018.
- Venetoclax (Venclexta) is a molecularly targeted therapeutic approved in November 2018.

Blastic Plasmacytoid Dendritic Cell Neoplasm

- Tagraxofusp-erzs (Elzonris) is a molecularly targeted therapeutic approved in December 2018.

Chronic Lymphocytic Leukemia and Small Lymphocytic Lymphoma

- Duvelisib (Copiktra) is a molecularly targeted therapeutic approved in September 2018.

Cutaneous T-cell Lymphoma

- Mogamulizumab-kpkc (Poteligeo) is an immunotherapeutic approved in August 2018.

Diffuse Large B-cell Lymphoma

- Polatuzumab vedotin-piiq (Polivy) is a molecularly targeted therapeutic approved in June 2019.

Follicular Lymphoma

- Duvelisib (Copiktra) is a molecularly targeted therapeutic approved in September 2018.
- Lenalidomide (Revlimid) is an immunomodulatory agent approved in May 2019 for use in combination with the immunotherapeutic rituximab (Rituxan).

Hairy Cell Leukemia

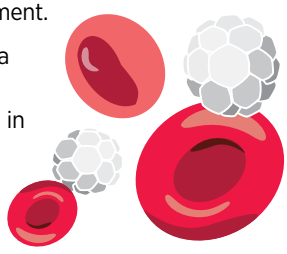
- Moxetumomab pasudotox-tdfk (Lumoxiti) is a molecularly targeted therapeutic approved in September 2018.

Marginal Zone Lymphoma

- Lenalidomide is an immunomodulatory agent approved in May 2019 for use in combination with the immunotherapeutic rituximab.

Multiple Myeloma

- ClonoSEQ assay is a next-generation sequencing–based test approved in September 2018 for determining whether a patient has minimal residual disease, or very low levels of cancer cells remaining, after treatment.
- Selinexor (Xpovio) is a molecularly targeted therapeutic approved in July 2019 for use in combination with dexamethasone.



At the same time as approving duvelisib for CLL/SLL, the FDA approved the therapeutic for treating certain patients with follicular lymphoma, a type of non-Hodgkin lymphoma that arises in B cells. The approval of duvelisib for treating patients with follicular lymphoma whose disease has progressed after they have received at least two other types of treatment was based on results from a phase III clinical trial. The results showed that 42 percent of patients whose disease was not responding to standard treatments had partial or complete tumor shrinkage following treatment with duvelisib.

Multiple myeloma is one of the most commonly diagnosed blood cancers in the United States, with 32,110 new cases expected to be diagnosed in 2019 (2). In recent years, the development and FDA approval of new therapeutics—including proteasome inhibitors like bortezomib (Velcade) and carfilzomib (Kyprolis), immunomodulatory agents such as lenalidomide (Revlimid), and immunotherapeutics such as the CD38-targeted daratumumab (Darzalex)—have improved outcomes for patients. Despite the advances, many patients whose disease initially responds to the new therapeutics eventually relapse due to treatment resistance.

In July 2019, the FDA approved a new molecularly targeted therapeutic called selinexor (Xpovio) for treating patients with multiple myeloma whose disease has relapsed subsequent to, or never responded to, treatment with at least two proteasome inhibitors, at least two immunomodulatory agents, and a CD38-targeted immunotherapeutic. Selinexor targets a protein called XPO1, which is found at elevated levels in multiple myeloma cells. XPO1 helps move proteins out of a part of the cell called the nucleus. It is particularly linked to moving proteins that suppress tumor growth out of the nucleus. When selinexor targets XPO1, it forces these proteins to be retained in the nucleus where they can act to suppress tumor growth. The approval of selinexor was based on results from a phase II clinical trial that showed that 25 percent of heavily pretreated patients responded to treatment with the new molecularly targeted therapeutic.

All of the molecularly targeted therapeutics for treating blood cancers that have been discussed above target specific molecules inside cancer cells. Three other molecularly targeted therapeutics approved by the FDA for treating blood cancers during the 12 months covered by this report target molecules on the outer surface of cancer cells (see **Figure 13,** p. 79). Polatuzumab vedotin-piiq (Polivy) is the most recently approved of these three therapeutics. It is an antibody-drug conjugate. Antibody-drug conjugates use an antibody to deliver an attached cytotoxic chemotherapeutic directly to the cancer cells with 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 cell. 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 polatuzumab vedotin-piiq, the cytotoxic agent monomethyl auristatin E is attached to a CD79b-targeted antibody. CD79b is found on the surface of immune cells called B cells, both normal B cells and those that become cancerous. Diffuse large B-cell lymphoma is an aggressive type of non-Hodgkin lymphoma that arises in B cells. It is the most common type of non-Hodgkin lymphoma diagnosed in the United States. Polatuzumab vedotin-piiq was approved for use in combination with the cytotoxic chemotherapeutic bendamustine and the immunotherapeutic rituximab for treating adults who have large B-cell lymphoma that has not responded to or has relapsed after two other treatments. The June 2019 approval was based on results from a phase Ib/II clinical trial that showed that 40 percent of patients who received all three of the anticancer therapeutics had complete tumor shrinkage compared with 18 percent of those who received only bendamustine and rituximab.

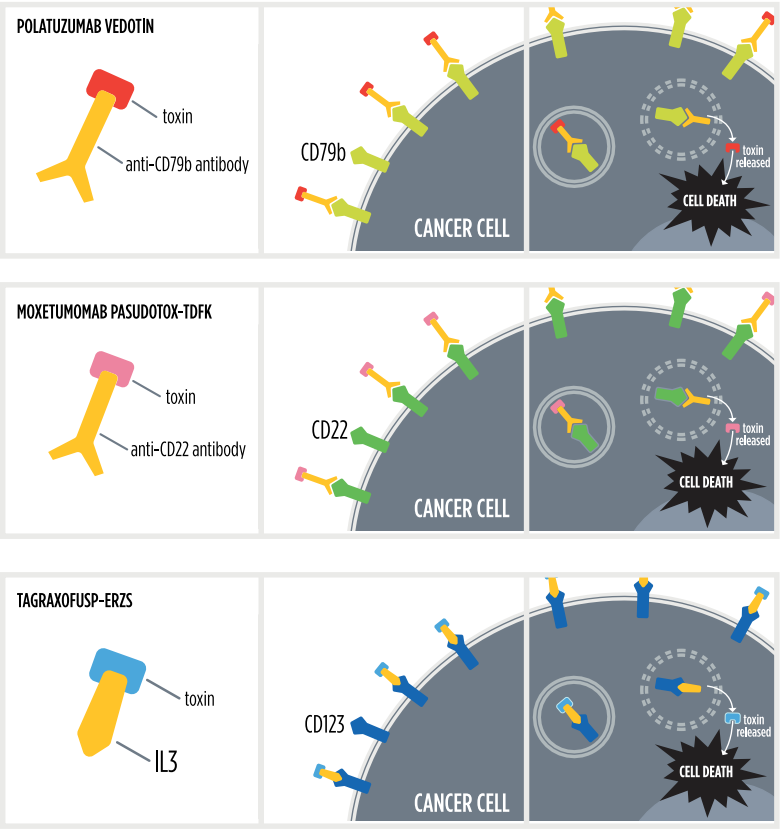
The other two therapeutics that target molecules on the outer surface of cancer cells, moxetumomab pasudotox-tdfk (Lumoxiti) and tagraxofusp-erzs (Elzonris), are cancer cell–targeted cytotoxins. These therapeutics work in a similar way to antibody-drug conjugates. They comprise two parts with different functions. As in antibody-drug conjugates, one part attaches to a specific molecular target on the outer surface of certain cancer cells, but the part in these therapeutics that kills cancer cells is a bacterial toxin, not a cytotoxic chemotherapeutic.

In the case of moxetumomab pasudotox-tdfk, the cytotoxin is a fragment of a toxin from *Pseudomonas aeruginosa* bacteria called Pseudomonas exotoxin A and the targeting portion attaches to CD22, a molecule on the outer surface of immune cells called B cells. Thus, CD22 is on the surface of most blood cancers that arise in B cells, including a rare type of slow-growing leukemia called hairy cell leukemia. The first treatment for most patients with hairy cell leukemia is the cytotoxic chemotherapeutic cladribine. Although this treatment often leads to durable remission, 30 percent to 40 percent of patients relapse after 5 to 10 years (221).

In September 2018, moxetumomab pasudotox-tdfk was approved for treating patients who have hairy cell leukemia that has not responded to or has relapsed after two treatments, including cladribine or another cytotoxic

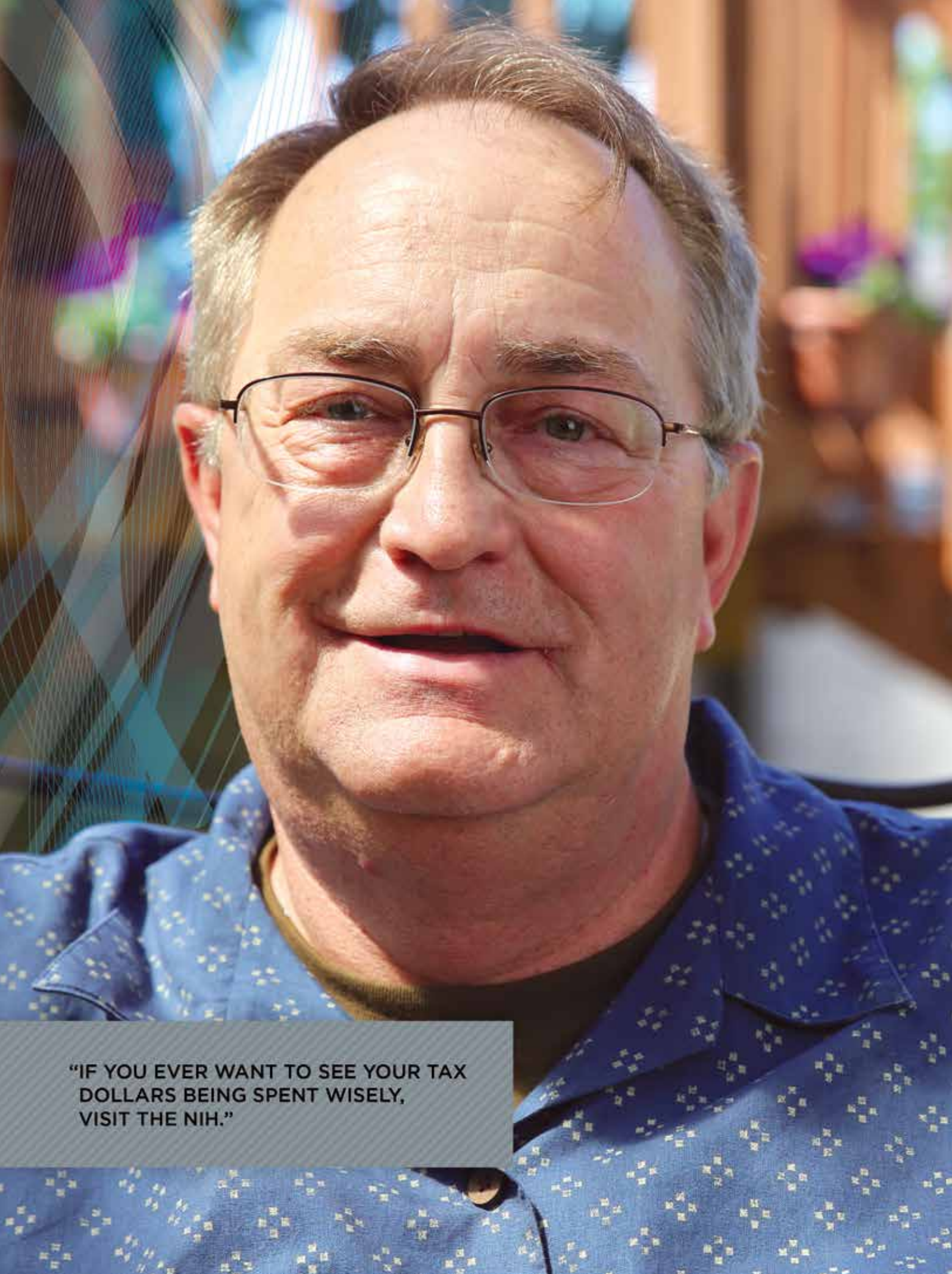
FIGURE 13

DELIVERING CYTOTOXIC AGENTS PRECISELY TO CANCER CELLS



Three molecularly targeted therapeutics approved by the U.S. Food and Drug Administration (FDA) during the 12 months covered by this report, August 1, 2018 to July 31, 2019, target molecules on the outer surface of cancer cells. Polatuzumab vedotin-piiq (Polivy) is an antibody-drug conjugate that consists of the cytotoxic chemotherapeutic monomethyl auristatin E attached to an antibody that targets the CD79b protein found on the outer surface of cancerous B cells. Once the antibody attaches to CD79b, the antibody-drug conjugate is internalized by the cell. This leads to the cytotoxic chemotherapeutic being released from the antibody. Once free, it is toxic to the cancer cells, which ultimately die. Moxetumomab pasudotox-tdfk (Lumoxiti) and tagraxofusp-erzs (Elzonris) are cancer cell–targeted cytotoxins that comprise a bacterial toxin connected to specific molecules that attach to specific proteins on the outer surface of cancer cells. These therapeutics work in a similar way to antibody-drug conjugates. In the case of moxetumomab pasudotox-tdfk, a fragment of a toxin from Pseudomonas aeruginosa bacteria called Pseudomonas exotoxin A is attached to an antibody that targets CD22, a protein on the outer surface of cancerous B cells. Tagraxofusp-erzs comprises parts of a toxin from Corynebacterium diphtheriae bacteria called diphtheria toxin attached to a protein called interleukin-3 (IL-3), which attaches to CD123, a protein located on the outer surface of blastic plasmacytoid dendritic cell neoplasm cells.

chemotherapeutic that works in the same way. The approval was based on results from a phase III clinical trial that showed that 30 percent of the patients who received moxetumomab pasudotox-tdfk had a durable complete response, which was defined as maintenance of hematologic remission for more than 180 days (222). Even though there are only about 1,000 new cases of hairy cell leukemia diagnosed each year in the United States (223), this approval provides a new treatment option and new hope for patients with the disease, such as **Randy Surratt** (see p. 80).


"IF YOU EVER WANT TO SEE YOUR TAX DOLLARS BEING SPENT WISELY, VISIT THE NIH."

RANDY SURRATT

AGE 62 | ROSEVILLE, MICHIGAN

LOOKING FORWARD TO THE FUTURE THANKS TO A CLINICAL TRIAL AT THE NIH

Since I was diagnosed with hairy cell leukemia 21 years ago, I have been in and out of treatment. Most recently, I was treated with moxetumomab pasudotox-tdfk (Lumoxiti) as part of a clinical trial being run at the National Institutes of Health (NIH). The six-month course of moxetumomab pasudotox-tdfk put me in complete remission for the first time since my cancer diagnosis and my blood counts have returned to normal for the first time in more than 15 years. I continue to live a day at a time, but my wife and I are now feeling more secure about the future.

I was diagnosed with hairy cell leukemia in August 1998, when I was 41. My wife, Vicki, had insisted I go to the doctor after I'd had several episodes of exhaustion over a hot and humid weekend. I'd tried to mow our lawn and been unable to do more than a couple of passes up and down before having to take a break. I also remember being too exhausted to walk back to the car without sitting down after throwing batting practice to my oldest son.

Two days after the doctor's visit, they called to tell me to go straight to the emergency room. They recommended that someone else drive me because the blood test results had shown that my blood cell and platelet counts were so low they were afraid I would pass out.

It took about a week to get the final diagnosis because hairy cell leukemia is so rare that the oncologist had wanted a second opinion from the University of Michigan before telling me. During that week, I was terrified. I didn't know anyone who was living successfully with cancer so I automatically thought I would not have long to live and I was extremely worried about what would happen to my wife and kids.

When they finally told me that I had hairy cell leukemia and that it was a slow-growing cancer that can be controlled by treatment, I felt some comfort. But they also told me that there was no cure, which was very hard on my entire family.

I started treatment with cladribine almost immediately. It is a chemotherapy that was given 24 hours a day for 7 days. The leukemia and the cladribine left my blood and platelet counts so low that my immune system was severely compromised and I had to remain in isolation in the hospital for three weeks while it rebuilt. As the general manager of a small family business, I kept my mind off everything by continuing to work from my hospital bed.

The cladribine put me in partial remission, but only for 2½ years.

Another cycle of cladribine put me back in partial remission, but it only lasted two years. At this point, I had two cycles of cladribine, but again, I was only in partial remission for about 2 years.

At this point, I changed treatment to rituximab (Rituxan). Unfortunately, like cladribine, this was only a temporary fix. Between 2005 and 2015, the leukemia would return every two years. Each time, rituximab would put me back in partial remission, but only for a limited time.

In 2015, my oncologist recommended I consider a clinical trial at the NIH testing a new treatment for hairy cell leukemia, moxetumomab pasudotox-tdfk. I had tried to enroll in the trial in 2005, but had not met the enrollment criteria. This time I did meet the criteria, and I was one of the last patients to enroll. From March 2016 to August 2016, I traveled to the NIH for monthly treatment with moxetumomab pasudotox-tdfk. A bone marrow biopsy taken 1 month after I finished treatment showed there was no sign of leukemia; I was in complete remission, and have been ever since.

Participating in the clinical trial at the NIH was a great experience. It was the first time I had ever met other patients with hairy cell leukemia, which helped me emotionally. It was also good to be cared for by nurses and oncologists who knew so much about the disease.

I am extremely thankful for having received moxetumomab pasudotox-tdfk, and I always say, "If you ever want to see your tax dollars being spent wisely, visit the NIH."

Tagraxofusp-erzs is a CD123-targeted cytotoxin. It comprises parts of a toxin from *Corynebacterium diphtheriae* bacteria called diphtheria toxin and a protein called interleukin-3 (IL-3), which attaches to CD123. CD123 is a molecule on the surface of blastic plasmacytoid dendritic cell neoplasm cells. Blastic plasmacytoid dendritic cell neoplasm is a rare type of blood cancer that is highly aggressive. Although many patients respond to treatment with a combination of cytotoxic chemotherapeutics, this treatment strategy ultimately fails to control the disease. The median survival of patients diagnosed with blastic plasmacytoid dendritic cell neoplasm is 8 to 14 months (224).

In December 2018, tagraxofusp-erzs became the first treatment approved by the FDA specifically for blastic plasmacytoid dendritic cell neoplasm. It was approved for treating patients who are age 2 or older after it was shown in an early-stage clinical trial that seven of 13 patients (54 percent) with previously untreated blastic plasmacytoid dendritic cell neoplasm who received the new CD123-targeted cytotoxin had a complete response (defined as disappearance of disease at each site of initial disease) or a clinical complete response (defined as a complete response with residual skin abnormality not indicative of active disease). A subsequent report on the trial that included results from a larger number of patients showed that 21 of 29 patients (72 percent) with previously untreated blastic plasmacytoid dendritic cell neoplasm had a complete response or a clinical complete response (224). In addition, 52 percent of the patients were alive 24 months after starting treatment with tagraxofusp-erzs.

Increasing Options for Patients with Prostate Cancer

Prostate cancer is the most commonly diagnosed cancer among men in the United States (2). It is also the second-leading cause of cancer death for U.S. men.

Most men who die from prostate cancer have metastatic disease. Therefore, 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 darolutamide (Nubeqa) recently became the third treatment approved by the FDA based on its ability to do the above.

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 have become the mainstay of prostate cancer treatment (bilateral orchiectomy or treatment with a gonadotropin-releasing hormone analogue agonist or antagonist) reduce androgen levels in the body, they do not eliminate these hormones completely. As a result, castration-resistant prostate cancer growth is still often fueled by androgens. Therefore, researchers have begun to develop a new generation of therapeutics that more effectively deprive prostate cancer of androgens. The first of these therapeutics, abiraterone (Zytiga) and enzalutamide (Xtandi), were approved by the FDA for treating men with metastatic castration-resistant prostate cancer in 2011 and 2012, respectively. Then, in 2018, the FDA approved enzalutamide and apalutamide (Erleada) for treating men with nonmetastatic castration-resistant prostate cancer.

The July 2019 approval of darolutamide provides men with nonmetastatic castration-resistant prostate cancer a third treatment option. The approval of this therapeutic was based on results from a phase III clinical trial that showed that adding darolutamide to standard androgen-deprivation therapy increased the time before prostate cancer metastasized by almost 2 years (225).

Expanding Treatment Options for Lung Cancer Patients

Lung cancer is the second most commonly diagnosed cancer in the United States, with more than 228,150 new cases expected to be diagnosed in 2019 (2). About 85 percent of lung cancers diagnosed in the United States are classified as non–small cell lung cancers (NSCLC).

In recent years, researchers have significantly increased our understanding of the genetic changes that fuel NSCLC growth in certain patients and have developed therapeutics that target some of these changes (226).

One of the genes most frequently mutated in NSCLC cancer is EGFR (226). Dacomitinib (Vizimpro) is a new EGFR-targeted therapeutic approved by the FDA in September 2018. It was approved as an initial treatment for patients with metastatic NSCLC that tests positive for certain EGFR mutations, either an EGFR exon 19 deletion or the exon 21 L858R mutation. The approval was based on results from a phase III clinical trial that showed that treatment with dacomitinib significantly increased the time to disease progression compared with gefitinib (Iressa), which is the EGFR-targeted therapeutic most commonly used to initially treat patients with metastatic NSCLC that tests positive for EGFR mutations (227). Such second-line treatments are

important because many NSCLCs that initially respond to molecularly targeted therapeutics eventually progress due to the development of treatment resistance.

In November 2018, the FDA approved a molecularly targeted therapeutic called lorlatinib (Lorbrena), providing a new option to help patients with NSCLC fueled by mutations in the ALK gene to address the challenge of treatment resistance.

The ALK gene is another gene frequently altered in NSCLC. Crizotinib (Xalkori) was the first ALK-targeted therapeutic to be approved by the FDA, in August 2011. It was followed by ceritinib (Zykadia), which was approved in April 2014; alectinib (Alecensa), which was approved in December 2015; and brigatinib (Alunbrig), which was approved in April 2017.

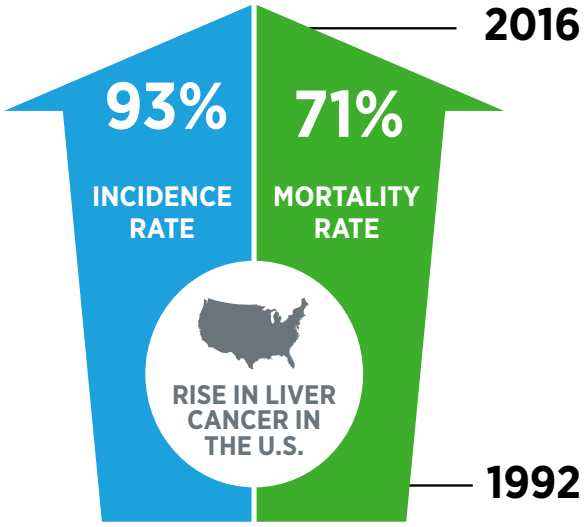
In many cases, resistance to crizotinib, ceritinib, alectinib, and brigatinib emerges because NSCLC cells acquire additional ALK mutations. Research has shown that the second-generation ALK-targeted therapeutics—ceritinib, alectinib, and brigatinib—can inhibit most of the ALK mutations that drive resistance to crizotinib and the third-generation ALK-targeted therapeutic—lorlatinib—can inhibit most of the ALK mutations that drive resistance to the second-generation ALK-targeted therapeutics (228).

Lorlatinib was approved for treating patients who have metastatic NSCLC driven by mutations in the ALK gene and whose disease has progressed despite treatment with crizotinib and at least one other ALK-targeted therapeutic for metastatic disease; treatment with alectinib as the first ALK-targeted therapeutic for metastatic disease; or treatment with ceritinib as the first ALK-targeted therapeutic for metastatic disease. The approval was based on results from a phase II clinical trial that showed that 48 percent of patients with ALK mutation–positive metastatic NSCLC who had previously been treated with one or more ALK-targeted therapeutics had complete or partial tumor shrinkage following treatment with lorlatinib (229).

As researchers seek to drive more progress against ALK-driven NSCLC, one area of intensive research investigation is determining the optimal sequence in which to use the five FDA-approved ALK-targeted therapeutics to provide the maximum benefit for patients.

Blocking the Blood Supply to Liver Cancer

Research has shown that many solid tumors need to establish their own blood supply and lymphatic vessel network to grow and survive. Identification of molecules that control the growth of new blood and lymphatic vessels within a tumor led to the development of therapeutics that specifically block them. These therapeutics are referred to as antiangiogenic agents.



From 2004 to 2015, the FDA approved 11 new antiangiogenic agents. These therapeutics are now approved for treating a wide array of cancer types (see **Supplemental Table 2,** p. 143). In the 12 months covered by this report, the FDA expanded the use of three of the antiangiogenic agents, cabozantinib (Cabometyx), lenvatinib (Lenvima), and ramucirumab (Cyramza) to include the treatment of a new type of cancer.

All three of the approvals have provided new treatment options for certain patients with the most common type of liver cancer, hepatocellular carcinoma. New approaches to treatment are urgently needed because the 5-year relative survival rate for liver cancer is 18 percent, which is one of the lowest 5-year relative survival rates for any type of cancer (2).

Most patients diagnosed with hepatocellular carcinoma that cannot be removed by surgery are initially treated with the antiangiogenic agent sorafenib (Nexavar). In August 2018, the FDA approved lenvatinib as an alternative treatment option for these patients. The approval was based on results from a phase III clinical trial that showed that overall survival among patients with hepatocellular carcinoma who were treated with lenvatinib was no worse than overall survival among patients who were treated with sorafenib (230).

Unfortunately, not all patients with hepatocellular carcinoma benefit from treatment with sorafenib or lenvatinib. Moreover, most patients whose tumors initially respond to these antiangiogenic agents eventually have disease progression.

In the first half of 2019, cabozantinib and ramucirumab were approved by the FDA for treating patients who have hepatocellular carcinoma that has progressed despite treatment with sorafenib. The approvals were based on results from phase III clinical trials that showed that the antiangiogenic agents improved overall survival compared with placebo (231).

TREATMENT WITH IMMUNOTHERAPY

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

The use of immunotherapeutics in the treatment of cancer is referred to as cancer immunotherapy. In recent years, it has emerged as the fifth pillar of cancer care and is one of the most exciting new approaches to cancer treatment that has entered the clinic. This is in part because some patients with metastatic disease who have been treated with these revolutionary anticancer treatments have had remarkable and durable responses. For example, recent long-term results from a clinical trial testing the immunotherapeutic pembrolizumab (Keytruda) as an initial treatment for patients with advanced NSCLC showed that 23 percent lived 5 or more years, which stands in stark contrast to the historical 5-year relative survival rate for patients with advanced NSCLC of about 5 percent (232).

Unfortunately, at present, only a minority of patients have such dramatic responses. In addition, current FDA-approved immunotherapeutics are not effective 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.

Fortunately, our scientific understanding of the immune system and how it interacts with cancer cells is rapidly increasing,

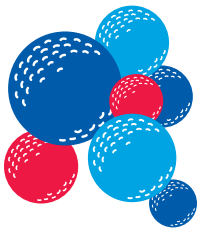
HOW IMMUNOTHERAPEUTICS WORK

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

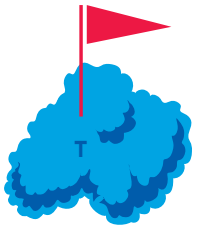
Some release the brakes on the natural cancer-fighting power of the immune system, for example, cemiplimab-rwlc (Libtayo), nivolumab (Opdivo), and pembrolizumab (Keytruda) (see **Releasing the Brakes on the Immune System,** p. 85).

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

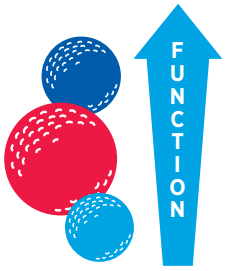
Some amplify the killing power of the immune system by providing more cancer-targeted immune cells called T cells, for example axicabtagene ciloleucel (Yescarta) and tisagenlecleucel (Kymriah).



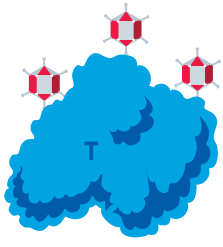
Some flag cancer cells for destruction by the immune system, for example mogamulizumab-kpkc (Poteligeo) (see **Directing the Immune System to Cancer Cells,** p. 91).



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



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



Adapted from (1)

and there are already clinical trials underway testing many novel immunotherapeutics and testing new ways to use those immunotherapeutics that we already have, such as combinations of those previously approved immunotherapeutics (233). One of the most promising advances is the development of a type of immunotherapy called adoptive T-cell therapy, which boosts the ability of the immune system to eliminate cancer cells (234) (see sidebar on **Types of Adoptive T-cell Therapy**). As of July 31, 2019, two of these new types of immunotherapy had been approved by the FDA, axicabtagene ciloleucel (Yescarta) and tisagenlecleucel (Kymriah). Both are a type of chimeric antigen receptor (CAR) T-cell therapy and are approved for treating certain patients with ALL and non-Hodgkin lymphoma. Early results from several small clinical trials suggest that researchers may have overcome some of the challenges to successfully developing CAR T-cell therapy for patients with certain solid tumors (235). However, more data from larger clinical trials will be needed to determine whether these new treatments provide significant benefit to patients and whether they have any long-term or late effects.

Clearly the new immunotherapeutics and treatment strategies that are on the horizon hold extraordinary promise for the future. Here, we focus on new immunotherapeutics that were approved by the FDA in the 12 months covered by this report, August 1, 2018 to July 31, 2019, and previously approved immunotherapeutics that were approved for use against additional types of cancer during the same period.

Releasing the Brakes on the Immune System

Research has shown that immune cells called T cells are naturally capable of destroying cancer cells. It has also shown that some tumors evade destruction by T cells because they have high levels of proteins that attach to and trigger "brakes" on T cells, stopping the T cells from attacking the tumor. These brakes, which are proteins on the surface of T cells, are called immune checkpoint proteins.

This knowledge led to the development of immunotherapeutics that release certain T-cell brakes (see **Figure 14,** p. 86). These immunotherapeutics are called checkpoint inhibitors. Two of the researchers whose work was pivotal to the identification of immune checkpoint proteins and their function, and to the development of checkpoint inhibitors, James P. Allison, PhD, and Tasuku Honjo, MD, PhD, were recognized with the 2018 Nobel Prize in Physiology or Medicine for their discoveries of cancer therapy by inhibition of negative immune regulation.

The first checkpoint inhibitor to be approved by the FDA was ipilimumab (Yervoy), in March 2011. This immunotherapeutic targets the immune checkpoint protein CTLA-4, protecting it from the proteins that attach to it and trigger it to put the brakes on cancer-cell killing by T cells.

TYPES OF ADOPTIVE T-CELL THERAPY

There are three main types of adoptive T-cell therapy (235). As of July 31, 2019, immunotherapeutics of only one type, chimeric antigen receptor (CAR) T-cell therapy, were 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 interact with the cancer cells.

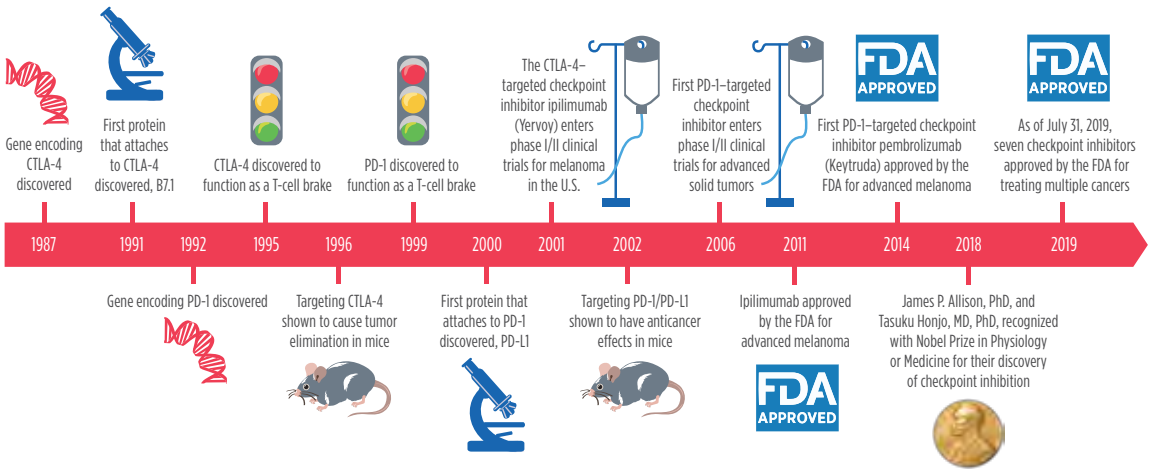
T-cell receptor (TCR) T-cell therapy.
T cells are harvested from a patient's blood and genetically modified in the laboratory to carry a new gene that encodes a protein called a TCR. The T cells are expanded in number and infused back into the patient. The TCR modification targets the T cells specifically to the patient's cancer cells and triggers them to attack when they encounter the cancer cells.

Tumor-infiltrating lymphocyte (TIL) therapy.
T cells are harvested directly from a patient's tumor, expanded in number in the laboratory, and infused back into the patient. Many of these T cells naturally recognize the patient's cancer.

Adapted from (1)

FIGURE 14

STOPS ALONG THE WAY TO DEVELOPING CHECKPOINT INHIBITORS



Checkpoint inhibitors are cancer immunotherapeutics that work by releasing "brakes" called immune checkpoint proteins on the surface of cancer-fighting immune cells called T cells. The first checkpoint inhibitor to be approved by the U.S. Food and Drug Administration (FDA) was ipilimumab (Yervoy), in March 2011. Ipilimumab targets an immune-checkpoint protein on T cells called CTLA-4. Several other checkpoint inhibitors target a second immune checkpoint protein called PD-1. The first of these immunotherapeutics to be approved by the FDA was pembrolizumab (Keytruda), in September 2014. More than 20 years of basic and clinical research underpinned the development of ipilimumab and pembrolizumab, starting with the discoveries of the CTLA-4 and PD-1 genes in 1987 and 1992, respectively (236)(237). Other basic research milestones along the way to the FDA approvals include the identification of the brake function of CTLA-4 and PD-1 (238-240), the identification of the proteins that attach to and trigger the brake function of CTLA-4 and PD-1 (241)(242), and the demonstration that immunotherapeutics targeting these brakes can protect them from being triggered (237)(243). Two researchers whose pioneering work established the paradigm of checkpoint inhibitors, James P. Allison, PhD, and Tasuku Honjo, MD, PhD, were recognized with the 2018 Nobel Prize in Physiology or Medicine for "their discovery of cancer therapy by inhibition of negative immune regulation.

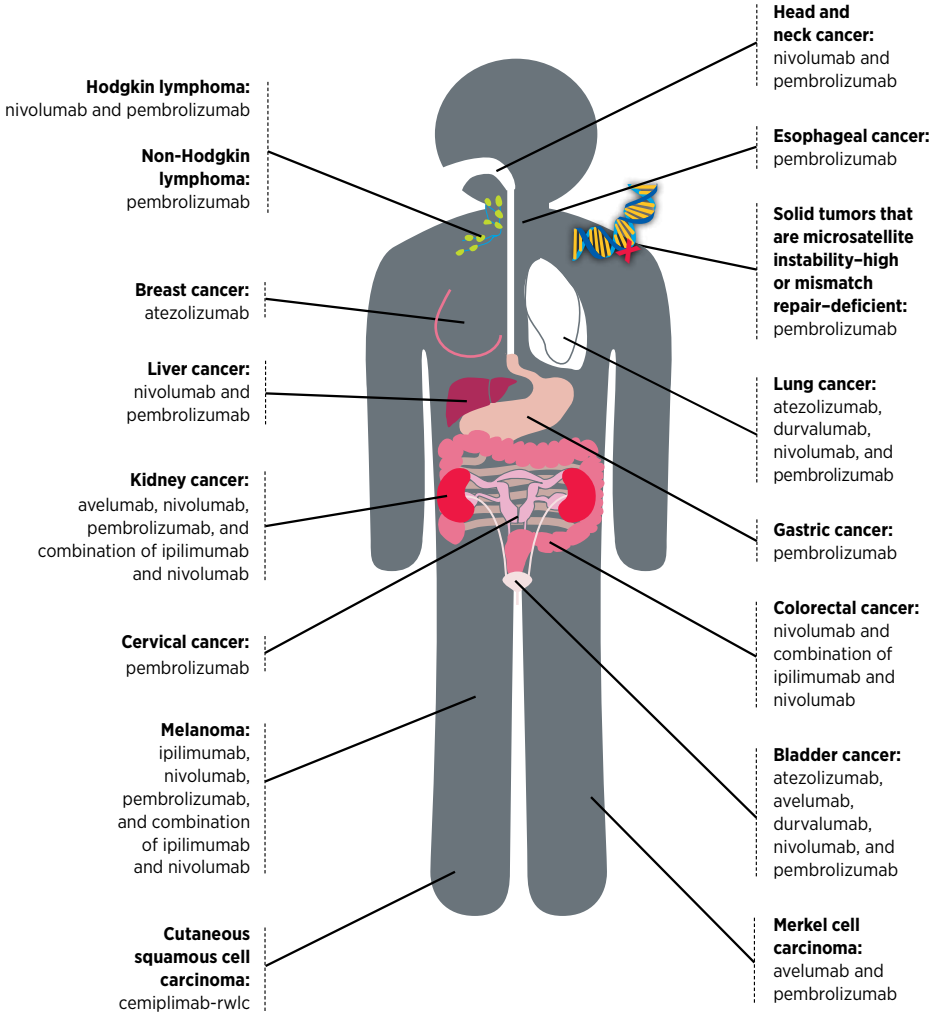
Adapted from (244)

Since the first approval of ipilimumab for treating patients with metastatic melanoma, the use of checkpoint inhibitors in the treatment of cancer has rapidly expanded. The FDA has approved six other checkpoint inhibitors, all of which 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. The FDA has also approved these groundbreaking immunotherapeutics for an increasingly broad array of cancer types. During the 12 months spanning this report, August 1, 2018 to July 31, 2019, the FDA approved one checkpoint inhibitor for the first time—cemiplimab-rwlc (Libtayo)—and expanded the uses of four of the previously approved checkpoint inhibitors—avelumab (Bavencio), durvalumab (Imfinzi), nivolumab (Opdivo), and pembrolizumab (Keytruda)—to include the treatment of additional types of cancer. As of July 31, 2019, there was at least one checkpoint inhibitor approved for treating 15 types of cancer and for treating any type of solid tumor characterized by the presence of specific molecular characteristics (see **Figure 15,** p. 87).

Cemiplimab-rwlc became the seventh checkpoint inhibitor approved by the FDA in September 2018. It was approved for treating patients like **Harold Sokoloff** (see p. 88) who have metastatic cutaneous squamous cell carcinoma or locally advanced cutaneous squamous cell carcinoma that cannot be treated with curative surgery or curative radiation.

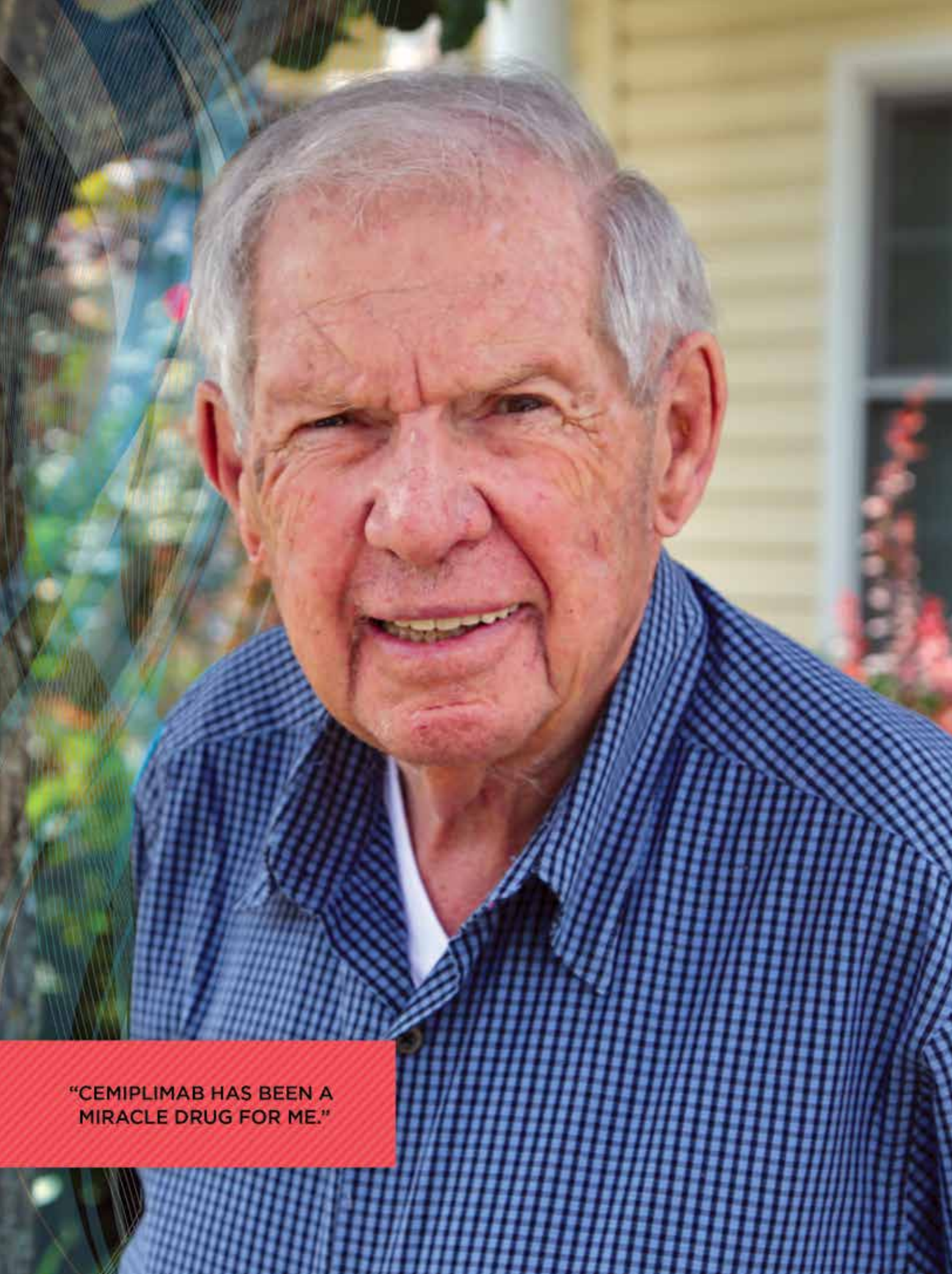
FIGURE 15

GOING DEEP WITH CHECKPOINT INHIBITORS



Checkpoint inhibitors are cancer immunotherapeutics that work by releasing certain "brakes" on the surface of immune cells called T cells, which are naturally capable of destroying cancer cells. The first 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), also for metastatic melanoma. Since then, another five checkpoint inhibitors have been approved by the FDA, atezolizumab (Tecentriq), avelumab (Bavencio), cemiplimab-rwlc (Libtayo), durvalumab (Imfinzi), and nivolumab (Opdivo). In addition, the FDA has expanded the number of cancer types for which there is at least one checkpoint inhibitor approved. The broad utility of these groundbreaking immunotherapeutics is highlighted by the fact that as of July 31, 2019, there was at least one checkpoint inhibitor approved for treating 15 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.

Adapted from (7)



"CEMIPLIMAB HAS BEEN A MIRACLE DRUG FOR ME."

HAROLD SOKOLOFF

AGE 93
PORT WASHINGTON, NEW YORK

BEATING CUTANEOUS SQUAMOUS CELL CARCINOMA THANKS TO CEMIPLIMAB-RWLC

I was diagnosed with locally advanced cutaneous squamous cell carcinoma in the fall of 2018; I was 92 at the time. Given my age, I thought that my body would not hold up well to surgery and radiation so I opted for a new treatment, cemiplimab-rwlc (Libtayo). It took only a few infusions with cemiplimab-rwlc for the cancer to be gone from view. It is miraculous, and I'm fortunate to be able to continue with my normal life.

Ever since my wife died from melanoma in 2002, I have taken great care to get regular checkups with my dermatologist. At my appointment in 2018, the dermatologist noticed an area of concern on the top of my head.

A biopsy showed that it was cutaneous squamous cell carcinoma, which is the second most common type of skin cancer. Because the cancer was large, I was told that it was considered locally advanced.

My dermatologist recommended that I see a surgeon who specialized in Mohs surgery, which is a common treatment for cutaneous squamous cell carcinoma. The Mohs surgeon told me that the cancer was so large that I would also need a plastic surgeon because I would need a skin graft once it had been removed.

A second doctor that I went to told me that six weeks of radiation was an alternative treatment option. This would have involved me going for treatment every day of the week for six weeks. There was no way I was going to do that at my age, I was 92 and it would have knocked me off my feet.

Fortunately my son learned that the FDA [U.S. Food and Drug Administration] had recently approved a new treatment for cutaneous squamous cell carcinoma called cemiplimab-rwlc. I made an appointment to see a doctor at Memorial Sloan Kettering Cancer Center and I started treatment with cemiplimab-rwlc in January 2019.

I go every three weeks to Memorial Sloan Kettering Cancer Center. After they have taken my vitals and I have spoken to the doctor, I get a 30-minute infusion of cemiplimab-rwlc. The only side effect I have had is itching, but I have cream for that and it does not bother me anymore.

Cemiplimab-rwlc has been a miracle drug for me. After just five or six infusions of the drug, which I call the potion, the cancer was no longer visible. In fact, I was just at my barber and he told me there was nothing he could see anymore.

After I have completed a year of cemiplimab-rwlc infusions, the doctors at Memorial Sloan Kettering Cancer Center will continue to monitor my progress and decide if and when to recommend additional treatment.

I know that we are continually making progress in medicine, with new drugs being developed all the time, but I feel very lucky that cemiplimab-rwlc was approved right before I needed it. That is why I believe that we need to continue to fund research because it is the only way to find new cures for many other diseases.

Cutaneous squamous cell carcinoma is the second most common type of skin cancer diagnosed in the United States. About 700,000 people were treated for the disease in 2012, which is the most recent year for which there are data (245). Most patients are cured by surgery and/or radiation. The emergence of advanced disease is rare. However, if it does occur, it can be difficult to treat and there were no therapeutics approved specifically to treat patients who were diagnosed with advanced cutaneous squamous cell carcinoma until the approval of cemiplimab-rwlc. The approval was based on results from two small clinical trials. Overall, 47 percent of the patients who received cemiplimab-rwlc had complete or partial tumor shrinkage. Most of these patients were continuing to gain benefit from the new checkpoint inhibitor at the time of its approval (246).

March 2019 marked another milestone in the era of checkpoint inhibitors. The FDA approved expanding the use of atezolizumab to include treating adults who have metastatic triple-negative breast cancer that tests positive for PD-L1 protein and adults who have locally advanced triple-negative breast cancer that cannot be removed by surgery and tests positive for PD-L1 protein. The approval was for the use of the checkpoint inhibitor in combination with the cytotoxic chemotherapeutic nab-paclitaxel (Abraxane). At the same time, the FDA approved the Ventana PD-L1 Assay as a companion diagnostic to identify patients with PD-L1–positive, triple-negative breast cancer.

Triple-negative breast cancer accounts for about 12 percent of breast cancer cases diagnosed in the United States each year (210). Breast cancers are classified as triple-negative if they test negative for hormone receptors and the protein HER2. Until the approval of atezolizumab, cytotoxic chemotherapeutics were the only systemic treatment options for patients with triple-negative breast cancer.

This groundbreaking approval was based on results from a phase III clinical trial that showed that adding atezolizumab to nab-paclitaxel significantly increased the time before disease progression compared with placebo and nab-paclitaxel (247). Early results from the trial suggest that treatment with atezolizumab and nab-paclitaxel also improves overall survival compared with placebo and nab-paclitaxel. Although more time is needed to determine the extent of the survival benefit, atezolizumab has already transformed the lives of many patients with triple-negative breast cancer, such as **Eva Joseph** (see p. 92).

Atezolizumab was approved for treating an additional type of cancer in March 2019. It was approved for use in combination with two cytotoxic chemotherapeutics, carboplatin and etoposide, for the initial treatment of adults diagnosed with extensive-stage small-cell lung cancer (SCLC). SCLC accounts for about 15 percent of lung cancers diagnosed each year in the United States (2). Most patients are diagnosed with extensive-stage disease, which means the cancer has spread beyond the lung, or the area between the lungs or the lymph nodes above the collarbone to other parts of the body. Even with treatment, which is commonly a combination of the cytotoxic chemotherapeutics carboplatin or cisplatin and etoposide, median survival is about 10 months. The approval of atezolizumab was based on results from a phase III clinical trial that showed that adding atezolizumab to standard treatment with carboplatin and etoposide significantly improved median overall survival (248).

In addition to the approval of atezolizumab for the initial treatment of adults diagnosed with extensive-stage SCLC, in the 12 months covered by this report, the FDA approved expanding the use of both nivolumab and pembrolizumab to include treating patients who have extensive-stage SCLC that has progressed despite treatment with a platinum-based cytotoxic chemotherapeutic and at least one other cytotoxic chemotherapeutic. The August 2018 approval for nivolumab was based on results from a phase I/II clinical trial that showed that nivolumab treatment led to partial or complete tumor shrinkage in 12 percent of patients whose disease had progressed after previous treatments. For pembrolizumab, the June 2019 approval was based on results from two clinical trials, one a phase I and the other a phase II, that showed that pembrolizumab treatment led to partial or complete tumor shrinkage in 19 percent of patients whose disease had progressed after previous treatments. Most of the patients benefited from nivolumab or pembrolizumab treatment for 12 or more months.

From August 1, 2018 to July 31, 2019, the use of pembrolizumab was also expanded by the FDA to include the treatment of certain patients with an additional four types of cancer. In July 2019, the FDA approved this checkpoint inhibitor for treating patients who have recurrent, locally advanced, or metastatic squamous cell carcinoma of the esophagus that tests positive for PD-L1 protein and that has progressed despite treatment with at least one other therapeutic. The approval was based on results from two clinical trials, one a phase II and the other a phase III. In the phase III clinical trial, pembrolizumab significantly improved overall survival compared with cytotoxic chemotherapy. In the phase II clinical trial, pembrolizumab treatment led to partial or complete tumor shrinkage in 20 percent of patients, most of whom benefited from the treatment for 12 or more months.

In November 2018, pembrolizumab was approved by the FDA for treating patients who have hepatocellular carcinoma that has progressed despite treatment with the molecularly targeted therapeutic sorafenib, which has been the standard of care for patients with this disease for more than a decade (see **Blocking the Blood Supply to Liver Cancer,** p. 83). The approval was based on results from a phase II clinical trial that showed that treatment with pembrolizumab led to partial or complete tumor shrinkage in 17 percent of patients (249). Most of these patients benefited from pembrolizumab treatment for 12 or more months.

A month later, in December 2018, the FDA approved pembrolizumab for treating certain patients with a rare, aggressive form of skin cancer called Merkel cell carcinoma. Specifically, it was approved for treating children and adults who have recurrent locally advanced or metastatic Merkel cell carcinoma after results of a phase II clinical trial showed that 54 percent of patients treated with pembrolizumab had complete or partial tumor shrinkage.

The other new FDA approval for pembrolizumab occurred in April 2019. The checkpoint inhibitor was approved for use in combination with the molecularly targeted therapeutic axitinib (Inlyta) for the initial treatment of patients who have advanced renal cell carcinoma, which is the most common type of kidney cancer. The combination of pembrolizumab and axitinib was approved after results from a phase III clinical trial showed that the combination significantly improved overall survival rates compared with sunitinib (Sutent), which is one of the most commonly used initial treatments for patients newly diagnosed with advanced renal cell carcinoma (250).

In May 2019, the FDA approved a second checkpoint inhibitor, avelumab, for use in combination with axitinib for the initial treatment of patients who have advanced renal cell carcinoma. The approval was based on results from a phase III clinical trial that showed that treatment with the combination of avelumab and axitinib significantly increased the time to disease progression compared with sunitinib (251).

Checkpoint inhibitors have yielded extraordinary benefit for patients with a diverse array of cancer types, but they can have adverse effects. The adverse effects arising from treatment with checkpoint inhibitors relate to the fact that these immunotherapeutics work by releasing brakes on the immune system. In a significant proportion of patients, this activation of the immune system leads to immune-related adverse effects. These adverse effects can affect any organ in the body and range from rash and local inflammation that can be treated with steroids and/or by temporarily discontinuing the treatment, to more severe adverse effects like thyroiditis and diabetes that need lifelong treatment with thyroid medications and insulin, respectively (252). If we are to predict which patients are likely to have severe immune-related adverse effects following treatment with a checkpoint inhibitor and design treatments to combat these effects without compromising the anticancer efficacy of the checkpoint inhibitor, we must better understand why and how the severe immune-related adverse effects arise. This is an area of intensive research investigation (252)(253).

Directing the Immune System to Cancer Cells

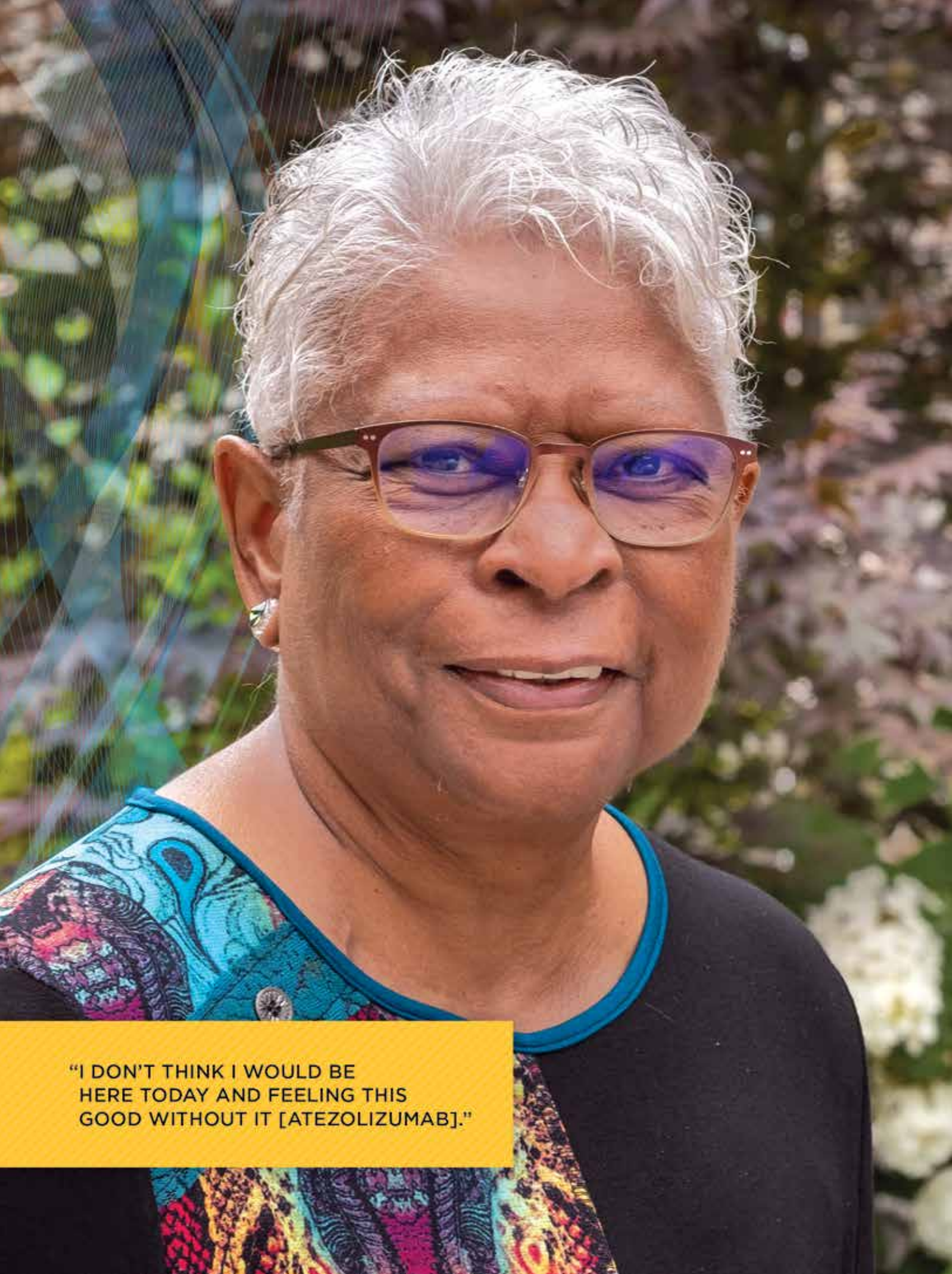
An immune cell must find a cancer cell before it can destroy it. Many immunotherapeutics that have been approved by the FDA for treating cancer work, at least in part, by helping immune cells find cancer cells (see **Cell Lysis Mediators** in **Supplemental Table 2,** p. 143). The most recent addition to this group of immunotherapeutics is mogamulizumab-kpkc (Poteligeo), which was approved by the FDA in August 2018 for treating certain patients with cutaneous T-cell lymphoma.

Cutaneous T-cell lymphomas are rare types of non-Hodgkin lymphoma that arise in immune cells called T cells. In these diseases, the cancerous T cells accumulate in the skin, resulting in an itchy, red rash. Mycosis fungoides and Sézary syndrome account for about two-thirds of the cases of cutaneous T-cell lymphomas diagnosed in the United States each year. In many cases, the cancerous T cells in patients with mycosis fungoides or Sézary syndrome have a protein called CCR4 on their surface. The newly approved immunotherapeutic mogamulizumab-kpkc targets CCR4. Once mogamulizumab-kpkc attaches to CCR4 on the surface of the cancerous T cells, it flags the cancer cells for destruction by immune cells.

The FDA approval of mogamulizumab-kpkc is for the treatment of adults who have mycosis fungoides or Sézary syndrome that has not responded to or has relapsed after treatment with at least one other treatment. The approval was based on results from a phase III clinical trial that showed that mogamulizumab-kpkc more than doubled the time to disease progression for patients compared with vorinostat (Zolinza), which is a standard treatment in this clinical setting (254).

One of the first immunotherapeutics to be approved by the FDA, rituximab (Rituxan), works, at least in part, by directing immune cells to cancer cells. Rituximab targets a protein called CD20, which is found on the surface of immune cells called B cells, both normal B cells and those that become cancerous. Since its first approval in 1997 for treating certain patients with a type of non-Hodgkin lymphoma called follicular lymphoma, which arises in B cells, it has been approved for treating several other types of non-Hodgkin lymphoma that arise in B cells and for treating CLL, which also arises in B cells.

Recently, researchers have been investigating whether combining newer anticancer therapeutics with rituximab can further improve outcomes for patients. In May 2019, the FDA approved a molecularly targeted therapeutic called lenalidomide for use in combination with rituximab for treating certain patients who have follicular lymphoma or another non-Hodgkin lymphoma that arises in B cells, marginal zone lymphoma. Specifically, the combination of lenalidomide and rituximab was approved for treating patients whose disease has progressed despite a previous treatment. The approval was based on results from two phase III clinical trials. In one of the trials, the time before disease progressed for patients with follicular lymphoma or marginal zone lymphoma that had progressed after initial treatment was almost three times longer among those who received lenalidomide and rituximab compared with those who received placebo and rituximab (255).



"I DON'T THINK I WOULD BE HERE TODAY AND FEELING THIS GOOD WITHOUT IT [ATEZOLIZUMAB]."

EVA JOSEPH

AGE 72 | WEST LINN, OREGON

KEEPING BREAST CANCER AT BAY WITH IMMUNOTHERAPY

After I was diagnosed with stage IV triple-negative breast cancer in July 2014, I was offered a place in a clinical trial testing a new treatment for exactly this type of cancer. I've been receiving regular infusions of an immunotherapy [atezolizumab; Tecentriq] and a chemotherapy [nab-paclitaxel; Abraxane] ever since, and the tumors in my lungs and sternum have shrunk dramatically. I don't think they will ever be gone, but I feel good. My husband and I enjoy going out; one of our favorite things to do is take a picnic basket to one of the wineries around here.

It all started in March 2002, when I went for my annual mammogram. It showed two spots on my left breast, which were confirmed to be cancer after a biopsy. I was very scared, and I didn't know what to expect. Was I going to die?

I first had a lumpectomy, but because the margins of the tissue around the cancer they removed were not clear of cancer cells, I had to have a mastectomy. During the surgery, they also removed the sentinel lymph node, which turned out to have cancer cells in it. This changed my diagnosis from stage II to stage III, and the surgery was followed by chemotherapy and then radiation.

The side effects of the treatment were awful. I was nauseous all the time and so tired I could barely walk anywhere. I was also depressed because I thought I looked bad; I had lost my hair and gained weight from the steroids included as part of the treatment. One of the things that helped me recover from the emotional side effects of the chemotherapy was redesigning my garden. I just felt stronger when I was working in the garden, and transforming it was quite beautiful and life affirming.

Our life slowly returned to normal, but in 2014, I started experiencing tightness in my chest and difficulty breathing. My primary care physician thought it might be a problem with my heart, but an X-ray showed that I had a lot of fluid on my lungs. It also showed why the fluid was there; the breast cancer had metastasized to my lungs.

After liters of fluid were drained from my lungs, I had a series of scans to see if the cancer had spread anywhere else in my body. Unfortunately, it had; the bone scan showed tumors in my sternum.

I was devastated by this turn of events. I thought stage IV breast cancer was a death sentence and that I was going to die imminently.

When I met with my oncologist to discuss my treatment plan, she recommended I enroll in the clinical trial testing an immunotherapy and chemotherapy combination as a treatment for patients with stage IV triple-negative breast cancer. I felt that it was my best treatment option and began receiving atezolizumab and Abraxane shortly after. I've been on this combination of treatment ever since.

After several rounds of treatment, I began to feel stronger and scans showed that the tumors in my lungs and sternum were shrinking.

Today, I feel good. I do have some nausea from the treatment, but it is nothing like the severe sickness I felt during my first chemotherapy in 2002, and my husband and I are able to enjoy short trips, which we couldn't back then. I wish I could say that the cancer is all gone, but I can't; however, the tumors are very small and my treatment is keeping them at bay. Considering that people diagnosed with stage IV triple-negative breast cancer are expected to live only about 18 months and I'm still here 4 years later, I'm doing very well.

I feel so fortunate to have had the opportunity to receive atezolizumab. I don't think I would be here today and feeling this good without it.

I want people to know that this new immunotherapy is providing hope for people like me, people who thought they had no chance to live, and that it only came about because of cancer research and the hard work and money that supported it.

SUPPORTING CANCER PATIENTS AND SURVIVORS

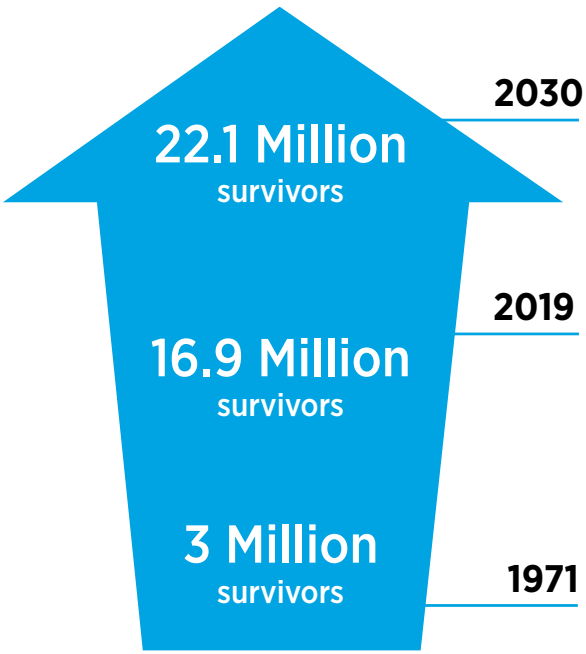
IN THIS SECTION, YOU WILL LEARN:

- In the United States, the number of people living with a history of cancer is expected to rise by 5.2 million in the next 11 years, reaching 22.1 million by January 1, 2030.
- Each person diagnosed with cancer faces a unique set of challenges, but one in four survivors reports a poor physical quality of life and one in 10 reports poor mental health-related quality of life.
- Palliative care, modifying behaviors, and cancer rehabilitation can improve quality of life.
- Improving implementation of palliative care, behavior modification, and cancer rehabilitation across the continuum of cancer care is essential if we are to better meet the needs of the rapidly expanding population of cancer 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. According to the latest estimates, more than 16.9 million U.S. adults and children with a history of cancer were alive on January 1, 2019, compared with just 3 million in 1971, and this number is projected to rise to 22.1 million by January 1, 2030 (3)(256). Meeting the needs of this rapidly expanding population will require a concerted effort from all stakeholders committed to reducing the morbidity and mortality of cancer, including advocates such as **Tomma Hargraves** (see p. 96), whose experience with lung cancer led her to train to become a patient lay navigator so that she could help others diagnosed with the disease.

While a person is considered a cancer survivor from the time of diagnosis through the remainder of his or her life, not everyone identifies with this term. Each person who is diagnosed with cancer has a unique experience. These experiences range from successful treatment and living cancer free for the remainder of life with or without adverse effects of treatment, to living with cancer and its effects for the remainder of life.

Cancer survivorship encompasses three distinct phases: the time from diagnosis to the end of initial treatment,



the transition from treatment to extended survival, and long-term survival. Each phase of cancer survivorship is accompanied by a unique set of challenges (see sidebar on **Life after a Cancer Diagnosis in the United States**). Importantly,

LIFE AFTER A CANCER DIAGNOSIS IN THE UNITED STATES

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

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

Although all cancer survivors face challenges, survivors of cancer diagnosed during childhood, adolescence, and young adulthood (from ages 0 to 39), are particularly at risk for severe long-term and late effects. The Children's Oncology Group's "Long-Term Follow-Up Guidelines for Survivors of Childhood, Adolescent, and Young Adult Cancers" were developed to help standardize and enhance the lifelong follow-up care of individuals who were diagnosed with cancer as children, adolescents, or young adults. For more information, see http://survivorshipguidelines.org/.

Adapted from (1)

the issues facing each cancer survivor vary, depending on many factors, including gender, age at diagnosis, type of cancer diagnosed, general health at diagnosis, and type of treatment received.

Unfortunately, certain segments of the U.S. population shoulder a disproportionate burden of the adverse effects of cancer and cancer treatment, which can negatively affect the duration and quality of life after a cancer diagnosis (see sidebar on **Disparities in Health and Quality of Life after a Cancer Diagnosis**, p. 98). In addition, a recent study found that these segments of the U.S. population were also at increased risk of experiencing financial hardship because of the out-of-pocket expenditures caused by a cancer diagnosis and cancer treatment (257). For example, 37 percent of cancer survivors who had no health insurance reported needing to borrow money, going into debt, declaring bankruptcy, or being unable to cover their copayments compared with 22 percent of cancer survivors who had private health insurance (257).

"THE BEST PART OF THIS ROLE [BEING A PATIENT LAY NAVIGATOR] IS THAT I SEE THE TREMENDOUS PROGRESS WE ARE MAKING AGAINST LUNG CANCER SINCE I WAS DIAGNOSED ALMOST 13 YEARS AGO."

TOMMA HARGRAVES

AGE 71 | RALEIGH, NORTH CAROLINA

CHOOSING TO HELP OTHER PATIENTS AFTER SURVIVING LUNG CANCER

After I was diagnosed with stage IIIB non-small cell lung cancer, I took part in a clinical trial testing an aggressive approach to treatment. It was a success, and I am a 12-year survivor. My experience led me to train to become a patient lay navigator. I love this volunteer role. By sharing with newly diagnosed patients what I learned through my experience with lung cancer, including how they should fear the tumor, not a trial, and by providing practical and emotional support to them, I am doing something positive and making a difference for others.

My journey with lung cancer began when I felt a little bump on the left side of my neck in October 2006. I was on my way to the beach and didn't think much about it at the time.

I did point the bump out to my primary care physician at a routine visit a few weeks later and he recommended a biopsy. I knew it must be bad news as soon as he called and asked me to come to the office to discuss the results. I did not want to wait so I asked him to tell me there and then. He told me I had non-small cell lung cancer and that I needed to have a CT scan right away. I was completely shocked. I couldn't believe it.

The scan showed a tumor in my upper right lung, and tumors in many lymph nodes in my mediastinum and on both sides of my neck. It meant that the cancer was stage IIIB.

I knew the survival statistics for patients with lung cancer were not good, so after a short trip to Florida with my husband, I sought opinions from several local cancer centers.

I opted to participate in a clinical trial at the University of North Carolina (UNC) Lineberger Comprehensive Cancer Center. I chose this because the trial was testing an aggressive approach to treatment that I felt would give me my best chance for survival. I was also impressed that the oncologist who met with me brought the whole care team, including the radiation oncologist, the pharmacist, and the nurse navigator, into the room to meet me.

The clinical trial started with high doses of chemotherapy, then changed to seven weeks of a higher than normal dose of radiation and lower doses of chemotherapy, and ended with several months of treatment with a new targeted therapy called erlotinib (Tarceva). The radiation was the hardest part for me. It caused burns and esophagitis, which prevented me from eating for three weeks, and has left my lungs permanently damaged. But that's a small price to pay for still being here.

At the end of the nine months of treatment, the oncologist told me that the cancer was gone. I was so full of joy that I hugged him, but I don't like to say that I'm cured or that my cancer is gone because you never know what will happen. I prefer to say that my cancer is controlled.

In fact, I did have a relapse in my lymph nodes and brain three years later, which chemotherapy and radiation were able to control. Since then, I have had no further treatments for the cancer.

Transitioning back to "normal" life after the nine months of active treatment was difficult, but being in the clinical trial meant that the team at UNC Lineberger kept following my progress. It was good to know that someone was watching me. Even now, I continue to have annual checkups for lung cancer because they help me emotionally.

A long-term effect of my treatment is that I can get pneumonia very easily because of the radiation damage to my lungs. As a result, when I get a cold I take antibiotics to guard against pneumonia. Apart from that, I'm great and I have switched direction from being a survivor to being a patient lay navigator and advocate.

Being a patient lay navigator at UNC Lineberger allows me to give back to the hospital that I credit with saving my life and being part of the team that supports patients who are newly diagnosed with lung cancer is incredibly fulfilling. The best part of this role is that I see the tremendous progress we are making against lung cancer since I was diagnosed almost 13 years ago. The new treatments that we have, which were made possible by cancer research, are giving more and more patients the chance to survive like I did.

DISPARITIES IN HEALTH AND QUALITY OF LIFE AFTER A CANCER DIAGNOSIS

Several segments of the population have been found to be disproportionately affected by cancer- and cancer treatment–related health complications that adversely affect health and quality of life after a cancer diagnosis. Examples of these disparities, which are a result of complex and interrelated factors (see sidebar **Why Do U.S. Cancer Health Disparities Exist?** p. 15), include the following:

TWO-FOLD INCREASED RISK	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 (259).
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 (260).
MORE THAN **TWICE**	Black women with breast cancer who were being treated with HER2-targeted therapeutics had more than twice the rate of heart damage (cardiotoxicity) as white women and therefore a significantly greater probability of incomplete therapy (261).
50% MORE LIKELY	Colorectal cancer survivors who had low socioeconomic status were 50 percent more likely to report clinically significant anxiety and depression compared with those who had high socioeconomic status (262).
23% MORE LIKELY	Cancer survivors who lived in rural areas were 23 percent more likely to report psychological distress compared with those in urban areas (263).

Financial hardship, or financial toxicity, extends beyond out-of-pocket direct medical costs and can be caused by indirect costs of lost productivity, such as days lost from work or disability days (263). Several recent studies have highlighted how this form of financial toxicity affects survivors of cancer diagnosed during adolescence or young adulthood (AYA) (ages 15 to 39) (264)(265). One showed that AYA cancer survivors have annual excess productivity losses of more than $2,000, and another showed that treatment type affects physical and mental work capacity and time off from work. For example, AYA breast cancer survivors who were treated with chemotherapy were more than twice as likely to take unpaid time off from work as those who were not treated with chemotherapy (265).

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

For patients and survivors with cancer, quality of life is a multidimensional concept that goes beyond the person's cancer-related outcomes and considers their overall physical, mental, emotional, and social functioning (266). As more and more people are surviving longer after a cancer diagnosis, the issue of quality of life has become increasingly important across the continuum of cancer care (267).

In recent years, numerous changes in cancer treatment are helping to reduce the short-term, long-term, and late effects

of treatment, and thereby improving quality of life for cancer patients and survivors (see **Progress across the Clinical Cancer Care Continuum,** p. 56). For example, molecularly targeted therapeutics more precisely target a patient's cancer cells compared with cytotoxic chemotherapeutics and therefore tend to cause fewer adverse effects, although longer follow-up of patients is needed to determine if molecularly targeted therapeutics have any long-term or late effects. In addition, health care providers and researchers are identifying ways to tailor surgery, radiotherapy, and cytotoxic chemotherapy to minimize their adverse effects without negatively affecting survival. The success of these approaches is highlighted by one recent study that found that significantly fewer survivors of cancer diagnosed in childhood are dying because of late effects of cancer treatment, such as a new cancer or heart disease, compared with three decades ago (268).

Despite advances in treatment that are helping improve quality of life, researchers have found that cancer survivors report lower general health and quality of life compared with people without a history of cancer (269)(270). For example, in one study, 25 percent of cancer survivors reported a poor physical quality of life and 10 percent reported a poor mental-health related quality of life compared with 10 percent and 6 percent of people without a history of cancer, respectively (269). Therefore, identifying new ways to improve general health and quality of life throughout a patient's experience with cancer, beginning at diagnosis and continuing through treatment, follow-up, survivorship, and end-of-life care, is an area of intensive research investigation.

Improving quality of life is also important because research suggests that quality of life is linked to cancer-related outcomes, including survival. In fact, several strategies, including outpatient specialty palliative care, integration of electronic patient-reported outcomes into routine oncology practice for symptom monitoring and management, and exercise, have been shown to improve quality of life and survival (271-274).

PALLIATIVE 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 and caregivers is palliative care (see sidebar on **What Is Palliative Care?**). 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 those who need it with 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 functional, psychological, social, and spiritual challenges that accompany a cancer diagnosis.

WHAT IS PALLIATIVE CARE?

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

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

Palliative care can be given in addition to cancer treatment or to those with no curative treatment options; palliative care given near the end of life when curative treatment has stopped is usually referred to as hospice care.

Palliative care is provided by a multidisciplinary team that works alongside the physicians treating the patient's cancer.

Palliative care is most widely available in hospital settings, but a team can also provide it at home, over the phone, or in an outpatient clinic.

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 (15)

Health care providers and researchers are constantly looking to identify new ways to palliate the physical symptoms and other adverse effects of cancer and its treatment. One strategy used to reduce the pain caused by cancer that has spread to the bones is palliative radiotherapy. In most cases, patients receive multiple doses of radiotherapy. However, recent results from a phase II clinical trial comparing the safety and effectiveness of a single high dose of stereotactic body radiotherapy and standard multifraction radiotherapy showed that significantly more patients who received a single high dose of stereotactic body radiotherapy reported relief from bone pain after 2 weeks, 3 months, and 9 months, compared with patients who received multifraction radiotherapy (275). In addition, the rate of recurrence of the treated bone metastases at both 1 and 2 years was lower among patients who received a single high dose of stereotactic body radiotherapy, suggesting that this may provide a new approach to palliating bone pain that requires fewer hospital visits, making it more convenient and effective for patients.

Recent research shows that integrating palliative care during the early stages of cancer care can significantly improve quality of life and significantly lower hospital costs (276-278). Thus, it is imperative that we increase awareness of the important role that palliative care can play across the continuum of clinical cancer care because many patients do not receive palliative care or even know what it is (279)(280).

PSYCHO-ONCOLOGY

Researchers and health care providers committed to developing new approaches to addressing the behavioral, emotional, psychological, and social challenges posed by cancer work in the field of psycho-oncology (see sidebar on **Helping Patients with Cancer through Psycho-oncology Research**). These challenges include treatment-related cognitive impairment, fear of cancer recurrence, anxiety, depression, stress, posttraumatic stress disorder, and feelings of despair. 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 (281)(282).

PROMOTING HEALTHY BEHAVIORS

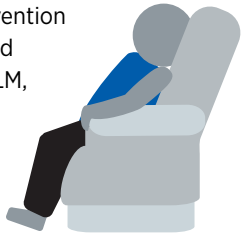
Evidence is emerging that modifying behaviors to eliminate or avoid many of the lifestyle-related factors that increase a person's risk of developing cancer and other chronic health conditions, such as cigarette smoking, inactivity, excess body weight, unhealthy diet, and alcohol consumption, can improve outcomes and quality of life for cancer patients and survivors (285-287) (see **Preventing Cancer: Identifying Risk Factors**, p. 24).

For example, research has shown that cancer patients and survivors who smoke cigarettes are at increased risk of cancer recurrence, developing a second cancer, treatment-related

HELPING PATIENTS WITH CANCER THROUGH PSYCHO-ONCOLOGY RESEARCH

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

A psychotherapeutic intervention called Managing Cancer and Living Meaningfully, or CALM, comprising three to six psychotherapy sessions lasting from 45 to 60 minutes, reduced symptoms of depression among patients with advanced cancer (284).



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 (285).

toxicity, poorer response to treatment, and death from cancer (57). Fortunately, all cancer patients and survivors who are current smokers can improve their prognosis by quitting smoking. Despite this knowledge, one study found that 9 percent of cancer survivors continue to smoke (288). Therefore, more research is needed to develop optimal strategies to provide patients with cancer who smoke with the best strategies for smoking cessation (289).

Research has also shown that eating a diet rich in vegetables, fruits, and whole grains, or a diet high in fiber, following a diagnosis of nonmetastatic colon cancer can reduce mortality (290)(291), and that exercising regularly or being physically active can reduce recurrence and mortality for survivors of several types of cancer, including early breast cancer, childhood cancer, colorectal cancer, and prostate cancer (292) (293). In addition, exercise can improve overall quality of life for patients and survivors who are undergoing treatment for cancer and for those who have completed treatment (294)(295). More specifically, exercise during and after treatment is completed has been shown to alleviate many of the adverse long-term and late effects of cancer and cancer treatments, including anxiety, depression, cognitive impairment, fatigue, lymphedema, pain, peripheral neuropathy, and poor sleep quality, and to improve heart and lung function (296-304). This burgeoning body of evidence has led experts to recommend that cancer patients and survivors achieve and maintain a healthy body weight, participate in regular physical activity, and eat a diet rich in vegetables, fruits, and whole grains (305).

CANCER REHABILITATION

General nutrition and physical activity guidelines can help cancer patients and survivors increase their chances of a better outcome and their chances of a higher quality of life. However, individuals diagnosed with cancer have their own unique needs for regaining and improving health. For many patients, these needs are not fully met by general guidelines, and this has led to an increasing recognition of the importance of cancer rehabilitation programs.

Cancer rehabilitation can improve quality of life by providing patients who need it with a tailored program of interventions to improve their daily function and quality of life (306). Cancer rehabilitation involves a multimodal, transdisciplinary team of health care professionals, which can include physiatrists, physical therapists, occupational therapists, speech-language pathologists, and rehabilitation nurses. After the team has identified an individual's personal cancer-related and cancer treatment–related impairments, they will develop a targeted treatment program to address the impairments (307). For example, interdisciplinary rehabilitation interventions that include a prosthesis, gait training, and impairment-specific therapeutic exercise can benefit patients who have a limb amputated as part of treatment for osteosarcoma; and medications and speech-language therapy can benefit patients who have changes in short-term memory or concentration after cancer treatment.

As discussed in **Treatment with Surgery** (see p. 60), there is growing recognition that intervening before (prehabilitation) and during active cancer treatment can promote recovery and reduce the incidence and/or severity of the symptoms and adverse effects of the disease and its treatment (308). For example, in one study, prehabilitation with a speech-language pathologist for education, baseline assessment of swallowing, nutrition, and prophylactic oral motor exercises helped reduce posttreatment swallowing and swallowing-related impairments for patients with head and neck cancer (309). In another study, prehabilitation consisting of home-based, moderate-intensity exercise reduced anxiety and increased physical functioning before and after surgery for men preparing to undergo radical prostatectomy after a prostate cancer diagnosis (310). In addition, numerous aspects of prehabilitation, including preoperative exercise, can benefit patients with breast cancer (190)(311), such as **Christine Cosby** (see p. 102).

Despite the emerging evidence that prehabilitation, enhanced recovery programs, and rehabilitation can improve quality of life across the continuum of cancer care, one recent study showed that only 1 percent to 2 percent of cancer survivors receive rehabilitation for cancer-related and cancer treatment–related impairments (306). This highlights the need for all stakeholders committed to reducing the morbidity and mortality of cancer to come together to ensure the efficient and effective integration of cancer rehabilitation services into the care of cancer patients and survivors. One recent study showed that the implementation of a collaborative telerehabilitation program consisting of 6 months of centralized telerehabilitation provided by a physical therapist–physician team improved function and reduced pain for patients who had advanced cancer (312). The program also reduced the time patients spent in hospitals and in long-term care facilities. Despite the success of this program, identifying the best way to implement cancer rehabilitation into the continuum of cancer care remains an area of intensive investigation in the increasingly important area of implementation research (306) (see sidebar on **What Is Implementation Research?** p. 104).

"...PREHABILITATION... IMPROVED MY FITNESS AND HELPED ME MAINTAIN A POSITIVE ATTITUDE THROUGHOUT TREATMENT."

CHRISTINE COSBY

AGE 52 | TORONTO, ONTARIO, CANADA

RECOVERING AFTER BREAST CANCER TREATMENT THANKS TO PREHAB AND REHAB

I was diagnosed with stage III breast cancer in March 2018. After the diagnosis and before my surgery, chemotherapy, and radiation, I participated in a pilot clinical study of prehabilitation that improved my fitness and helped me maintain a positive attitude throughout treatment. I experienced a lot of side effects from my treatments, so my medical team referred me to a rehabilitation program. Both prehab and rehab benefited me physically and mentally, and today I am slowly but surely recovering.

My cancer journey began when I felt a lump in my right breast. I was sent for a mammogram and an ultrasound by my primary care physician. This was followed by a biopsy at the rapid diagnostic center at Princess Margaret Cancer Centre.

Just a few days later, my husband and I met the oncologist to learn the results from the biopsy. I was overwhelmed to hear that I had breast cancer. There is no history of the disease in my family, so this was totally out of the blue.

Right after giving us the devastating news of my cancer diagnosis, the oncologist outlined my treatment options. I decided I would have a full mastectomy; they would remove my entire right breast and many of the lymph nodes under my right arm.

We next met with a researcher who talked to us about a pilot clinical study of a prehabilitation exercise program. She explained to us that the idea is that participating in the exercise program before breast cancer surgery can help recovery. Being told that there was something positive that I could do to help myself was very appealing and I was motivated to sign up. I also believe that it is important to support research that will help patients in the future.

There were only two weeks between my diagnosis and surgery, but taking part in the prehab program gave me something positive to focus on and distracted me somewhat from my fears of the upcoming treatment.

The researchers provided me with a simple exercise program after they had taken some baseline measurements of my grip strength and cardio fitness. I was shown how to do five exercises with a resistance band, which I could do at home to build my upper body strength, and I was told that running up the steps at my neighborhood park for 10 or 20 minutes a day would improve my cardio fitness.

I had a tracking sheet to log my progress and this helped motivate me to exercise almost every day before the surgery. I know that the prehab improved my physical fitness because right before the surgery they repeated the grip strength and cardio fitness measurements and both had improved. It also taught me that a little exercise goes a long way, which has helped me enormously because I now know that I only need to take small steps to gain benefit.

The time after surgery is a bit of a blur for me. I had eight cycles of chemotherapy from May until August and then 25 radiation treatments from August to October. Since then, I've been taking letrozole every day.

I struggled badly with side effects from the treatments, in particular pain, fatigue, and lymphedema. As a result, my medical team referred me to an eight-week group rehabilitation program. There were 10 of us in the weekly classes, which introduced us to new strength and cardio exercises, and provided us with information on nutrition, mental health, and brain health. I also began physiotherapy and massage to help manage the pain and the lymphedema.

Overall, I feel that the prehab and the rehab programs really benefited my body and my mind. Physically, I saw improvement in my pain and fatigue almost as soon as I started the rehab program, and I know that my strength and cardio fitness are better than before surgery. Being able to see the physical progress also helps mentally; it helps me maintain a positive attitude, even when I experience setbacks.

Today, there is no sign of cancer in my body and I've recovered enough to go back to work part time. This has taken time away from my exercise program, but I'm learning to balance work, exercising, and socializing. My husband and I spend a lot of time together, and we just keep celebrating every day.

WHAT IS IMPLEMENTATION RESEARCH?

According to the National Cancer Institute, implementation research is the study of methods to promote the adoption and integration of evidence-based practices, interventions, and policies into routine health care and public health settings to improve the impact on population health (314).

Implementation research can help bridge the divide between research and clinical cancer care because interventions that have proven effective in clinical trials for preventing cancer, reducing cancer incidence and mortality, and improving quality of life are only truly effective if they are delivered to those who need them.

When implementing an evidence-based intervention, such as colorectal cancer screening or an exercise intervention for cancer patients and survivors, it is important to:

Assess whether the evidence-based intervention will fit the goals and needs of all stakeholders affected by its implementation, including the health care providers who would have to deliver the intervention and the cancer patients and survivors who would receive it.

Prepare a plan to implement the evidence-based intervention in the community to be served by using information from the assessment step to determine the education, training, and workflow-change needs of the stakeholders.

Implement the plan by changing workflow practices, training health care providers in how to deliver the evidence-based intervention, and educating and engaging the community the intervention is designed to benefit.

Evaluate whether the evidence-based intervention was fully implemented or whether the implementation plan needs adapting to improve uptake.

DELIVERING CARE TO CANCER SURVIVORS

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

COORDINATING CARE

Most cancer survivors have poorer health and quality of life than other individuals of a similar age and are at increased risk for long-term morbidity and premature mortality as a result of their cancer diagnosis and treatment. Therefore, cancer survivors have complex health-care needs that are best met by a wide range of health care professionals.

Emerging evidence suggests that cancer survivors receive the highest level of care if their care is well coordinated, either by an oncologist and primary care provider or shared by multiple specialists (267)(314). Given that the follow-up cancer care needs of each survivor are unique, we need to identify the optimal way to provide comprehensive, coordinated, patient-centered care to all cancer survivors, rather than using a one-size-fits-all approach (315).

THE IMPORTANT ROLE OF CAREGIVERS

Caregivers provide an extension to a cancer survivor's health care team, playing a vital role across the continuum of cancer care, from diagnosis through long-term survivorship. The population of caregivers is growing proportionally with the number of cancer survivors. One recent study of caregiving in 18 U.S. states led researchers to estimate that there are 1.1 million family caregivers of adults with cancer living in these states and that more than one in five of these people provided caregiving for more than 20 hours per week (316).

It is important to note that all caregivers are at risk for poor health outcomes, in particular, poor mental health outcomes (285). However, research shows that those who provide caregiving for longer hours experience worse outcomes (316). Such research is bringing increasing awareness to the need for new strategies to optimize and tailor support for caregivers.

LOOKING TO THE FUTURE

IN THIS SECTION, YOU WILL LEARN:

- Innovations in cancer research through interdisciplinary team science approaches will help shape the future of patient 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.
- Cutting-edge technologies that fuel the full spectrum of cancer science from bench to bedside will accelerate the pace at which we increase our understanding of cancer biology while transforming the future of clinical practice.

This is an exciting era of cancer research. Approval of novel therapeutics, coupled with an increasing public awareness of cancer prevention and early detection, has led to dramatic reductions in overall cancer mortality rates for all Americans. Recent discoveries in the fields of cancer genomics and immunology have firmly established two new pillars of cancer care—molecularly targeted therapy and immunotherapy—which are benefiting many patients with a wide range of cancer types.

These research fields also show immense promise for the future because the pace of progress in these areas is expected to accelerate in the coming years. However, to efficiently harness the information generated by cancer genomics and immunology research, it will be essential to engage scientists across disciplines who can translate these data into clinical benefit for more patients. According to **AACR President, 2019–2020, Elaine R. Mardis, PhD,** a convergence science approach, which merges traditional basic and clinical cancer research with applied mathematics, engineering, and physics, among other disciplines, will pave the way for the next breakthroughs in cancer science (see p. 106). The new wave of scientific and technological innovations driven by cross-disciplinary team science will have a transformative impact on patient care.

TECHNOLOGIES TO ADVANCE CANCER SCIENCE

SINGLE CELL TECHNOLOGIES

Decades of research have led scientists to realize that tumors are a collection of highly heterogeneous cancer cells as well as other cell types. There is heterogeneity in genetic alterations between different cancer cells within a tumor as well as between primary and metastatic tumors. There is also cellular diversity within tumors, which comprise many different types of cells including immune cells and endothelial cells that make up blood vessels, in addition to cancer cells. Genetic heterogeneity within tumors contributes to treatment resistance and disease recurrence while interactions between cancer and immune cells within a tumor can influence response to treatments such as immunotherapy.

Past efforts at evaluating cellular and molecular characteristics of cancer used "bulk" analysis, which meant that multiple cell populations from the tumor mass or biopsy sample were profiled simultaneously. Although this approach provided many useful insights, it did not provide highly detailed information about the subtle differences between cells. Single cell technologies have ushered in a new era for medical research including cancer research. By using these techniques, researchers are able to quickly analyze molecular

"RESEARCHERS STRIVE TO HARNESS ADVANCES IN TECHNOLOGY NOT ONLY TO ACCELERATE THE PACE OF BASIC RESEARCH, BUT ALSO TO IMPROVE PATIENT CARE."

ELAINE R. MARDIS, PHD

AACR PRESIDENT, 2019–2020
Co-Executive Director, Institute for Genomic Medicine, Nationwide Children's Hospital, Columbus, Ohio

ENVISAGING TECHNOLOGICAL INNOVATION THROUGH CROSS-DISCIPLINARY TEAM SCIENCE

Over the past 30 years, I have witnessed firsthand the coming of age of the field of cancer genomics research and its clinical applications. This field of basic research led to the development of a powerful new approach to cancer treatment decision-making, called precision medicine. Continued increases in federal funding for research will allow us to support more cross-disciplinary team science, sparking a new wave of technological innovation and associated discoveries that will have a major impact on future progress across the clinical care continuum.

As a doctoral student, I worked in one of the few academic laboratories in the United States to apply DNA sequencing to human disease research, including cancer. Back then, we decoded single genes that were involved in cancer, as a means of better elucidating their role in the disease. Now, as a result of incredible technological advancements, almost every academic laboratory in the country is using modern-day genomic methods and instrumentation to address questions in biomedical research.

Among the breakthroughs that were made possible by these remarkable advances in our capacity to sequence DNA were the sequencing and analysis of the human genome, and the accurate sequencing and analysis of the genomes of many types of pediatric and adult cancers. Moreover, these new sequencing technologies and the associated analytics have made it to the bedside; many clinics and commercial testing providers use genomic profiling of a patient's tumor to identify disease-causing mutations, to refine diagnoses, and to guide patient treatment.

The emergence of precision medicine is just one example of how a better understanding of cancer as a disease can ultimately lead to advances for patients. In fact, everything we do today to take care of people with cancer is built on decades of basic research.

Moving forward, increasing the integration of researchers from diverse disciplines, including engineering, mathematics, and computer sciences, into the cancer field will be highly impactful. It will help us to use the huge amounts of data we are collecting in genomics, clinical outcomes, and other areas in order to computationally model cancer development and progression. This, in turn, will allow us to begin to interpret every patient as an individual entity and to determine how best to treat each one.

A cross-disciplinary approach to cancer research will also drive further technological advancements. One cutting-edge technology that is poised to transform our understanding of cancer and, ultimately, patient care, is single cell sequencing. This new approach that characterizes single cells from cancers is being complemented by studies of single cells from normal human tissues (Human Cell Atlas), revealing nuances that better define our understanding of how cancer cells compare to normal cells. This is revolutionary because historically, in studies of human disease, we have neglected to characterize or contextualize normal tissues. Knowing these baseline values will make our understanding of what is abnormal so much richer.

Cutting-edge gene-editing technologies, such as CRISPR/Cas9, are also primed to drive progress in the near future. These technologies are giving us the power to understand the impact of the genetic mutations we detect through cancer genomics research in ways that have never been possible. They also are permitting large-scale screening of unknown mutations in the context of anticancer therapeutics to identify vulnerabilities for specific drug-gene combinations. Both approaches are pivotal for developing new strategies for treating cancer. Gene-editing technologies are also being used in an actively growing area of basic research that promises to deliver new engineered immune cell therapies for both adults and children with cancer.

Researchers strive to harness advances in technology not only to accelerate the pace of basic research, but also to improve patient care. Liquid biopsies are one technology-aided approach that may be applied in many different ways in the clinical diagnosis and monitoring of cancer patients. For example, we are investigating whether we can track the response of pediatric brain cancer patients to therapy through genomic analysis of a small amount of cerebral spinal fluid.

Early detection of cancer is another area in which liquid biopsy methods could have a major impact, because the earlier a cancer is detected the more likely it can be treated successfully. There are still a lot of questions to be answered and barriers to overcome if we are to realize this potential use of liquid biopsies, but I believe we will get there through cross-disciplinary studies that include radiologic imaging, surgery, and genomics.

If we are to encourage the cross-disciplinary team science approach to cancer research that is key for igniting technological innovation and advances against all pediatric and adult cancers, we need robust annual increases in federal funding for research. These resources are vital if we are to pave the way for the next major breakthroughs that will transform patient care.

characteristics of single cells, and by combining data from hundreds or thousands of single cells from a tumor, they can obtain a better understanding of its heterogeneity (317).

There are many different single cell technologies, but their end-goal is the same: to help researchers understand the biological role of each type of cell in a tumor. For example, some researchers hope to differentiate the characteristics of cancer cells from immune cells, and to determine if the immune cells in the tumor are helping the cancer grow or are attacking it. Others are attempting to map the 3-dimensional location of cancer cells and other cell types within the tumor microenvironment by pairing single cell technologies with the latest advanced imaging strategies (318). Spatial details extracted from such studies can be invaluable in understanding the interactions between cancer and other cells and the tumor microenvironment, which plays a key role in tumor growth and metastasis.

GENE EDITING

Next-generation sequencing technologies have revolutionized the field of cancer genomics. As a result, we have identified numerous genetic alterations that are associated with cancer development. However, to confirm whether a genetic alteration can lead to cancer development, scientists need to determine the functional consequences of these genetic changes. Gene editing through CRISPR/Cas9 is a revolutionary approach that can help researchers add in a specific mutation of interest, and then study the functional outcomes of the mutation and its impact on biology (319). These methods provide a fast, precise, scalable, and efficient approach to gene editing compared with previous technologies. The development of CRISPR technology resulted from basic research into the immune system mechanisms of certain species of bacteria (320). CRISPR technology is being currently used by researchers throughout the medical 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 immunotherapy with CAR T cells (321).

TECHNOLOGIES TO ADVANCE PATIENT CARE

The new therapeutic and diagnostic technologies that are moving rapidly from the bench to the bedside have the potential to fundamentally change cancer care in the future.

LIQUID BIOPSIES

A biopsy is the removal of cells or tissues from a patient for testing to help physicians diagnose a condition such as cancer or monitor how it changes in response to treatment. Traditionally, biopsies are invasive procedures. However, research has shown that during cancer development and treatment, tumors routinely shed detectable cells, lipid-encapsulated sacs called exosomes, and free DNA into a patient's blood or cerebrospinal fluid. Recent studies have also shown that it is possible to use a blood or another biofluid sample, or liquid biopsy, rather than a traditional tissue biopsy, to obtain material that can be analyzed to provide information about the molecular alterations associated with a patient's cancer (322).

Multiple liquid biopsy approaches to improve cancer screening, early detection, and monitoring of treatment response are being developed and tested in clinical trials (see sidebar on **Moving toward Minimally Invasive Testing,** p. 109). Some of these focus on analyzing blood samples for mutations in the DNA sequence or epigenetic changes associated with cancer, while others look more broadly at the patterns of fragmentation of the shredded cell-free DNA in the blood (323-325). Early clinical data indicate that liquid biopsies have the potential to transform early detection, interception, diagnosis, treatment, and surveillance of cancer by identifying markers of disease, therapeutic response, resistance, and recurrence (326-328).

BIG DATA

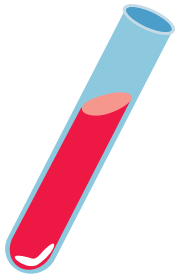
To achieve the full potential of cancer genomics research, the molecular characteristics of a patient's cancer need to be considered along with other factors, such as the patient's genome, epigenome, microbiome, metabolome, lifestyle, and environmental exposures, all of which are emerging as important influences on cancer initiation, development, and progression. Integrating and harnessing data that include patient history, results from diagnostic and genetic tests, treatment decisions, and measured and patient-reported

In May 2019, the FDA approved the second liquid biopsy companion diagnostic test which detects PIK3CA mutations in individuals with HER2-negative, advanced or metastatic breast cancer.

MOVING TOWARD MINIMALLY INVASIVE TESTING

Liquid biopsy refers to the collection and analysis of biofluids, such as blood, cerebrospinal fluid, or urine. In oncology, it primarily involves the capture and analysis of cells, lipid-encapsulated sacs called exosomes, or free DNA shed by tumors. 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.

- Liquid biopsies have the potential to be safer and less invasive for the patient, more likely to result in patient compliance, and better representative of tumor heterogeneity than a typical biopsy.
- Currently, liquid biopsies are used in the clinic to a) detect mutations in cancers that are targetable by therapeutics, and b) detect mutations in cancers that may indicate the emergence of resistance to certain therapeutics.
- Ongoing research is further assessing the value of liquid biopsies in a) detecting early evidence of disease; b) monitoring disease burden; c) evaluating response to treatment, including treatment with immunotherapeutics; and d) evaluating tumor heterogeneity.



outcomes from large numbers of cancer patients may help us 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 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 AACR Project Genomics, Evidence, Neoplasia, Information, Exchange (GENIE), ASCO CancerLinQ, BRCA Exchange, NCI Genomic Data Commons, and Oncology Research Information Exchange Network (ORIEN) (329). Continued advances in technological innovations as well as regulatory policy initiatives will be critical to overcome current barriers to data sharing and create a framework for a global data ecosystem that will accelerate discoveries and benefit patient care.

ARTIFICIAL INTELLIGENCE

As we accumulate large quantities of patient data, artificial intelligence (AI) approaches, such as machine learning, have the potential to help us analyze vast amounts of health care information to derive meaningful insights that we previously could not have realized (330). Machine learning is an application of AI that focuses on the development of computer programs that can access and learn from data, identify patterns, and make decisions without explicit human intervention.

The clinical applications of AI are vast. For example, some of the recent approaches in liquid biopsy rely on AI to detect cancer in the blood. Other examples of the use of AI in patient care include radiological imaging analysis and pathology testing results determination, both of which are critical in diagnosing cancer. Traditionally, the former involves a radiologist scanning images by visually searching for signs of cancer while pathology testing involves a pathologist viewing a slide on which there is a slice of the abnormal tissue under a conventional light microscope to determine the presence of cancerous cells. Current methods of analyzing scans and slides are time consuming and can sometimes miss signs of cancer (false negative) or detect cancers that turn out to be imaging artifacts (false positives). AI has the potential to streamline processes for radiological and pathological image interpretation allowing for faster decision-making for people with life-threatening diseases. The applications of AI in radiology and pathology are an area of extensive research (331-334). Continued research is needed to determine the full clinical potential of AI along with appropriate regulatory approaches to ensure safety and efficacy of this novel technology.

THE FUTURE OF TREATMENT COMBINATIONS

A potential application of big data and machine learning in advancing future cancer treatments will be in the identification of combinations of therapeutics to treat cancers. Although molecularly targeted therapeutics and immunotherapeutics have transformed the landscape of cancer care, only a small fraction of patients respond to these treatments and most tumors eventually develop resistance to these agents (see sidebar on **The Challenge of Treatment Resistance,** p. 72). As a way of

starting to address these challenges, the FDA has approved combinations of molecularly targeted therapeutics, such as encorafenib and binimetinib for treatment of melanoma or combination of a molecularly targeted therapy with immunotherapy, such as pembrolizumab and axitinib for the treatment of kidney cancer.

These so-called rational combinations of therapeutics are based on our understanding of cancer initiation, progression, resistance, and/or recurrence. Combination of therapeutics within and between various treatment modalities, such as immunotherapy, molecularly targeted therapy, and cutting-edge radiotherapy, is being tested in many clinical trials against a wide array of cancers. Given that the number of potential combinations of treatments is already immense and will increase dramatically as the number of cancer therapeutics rises in the future, continued research is needed to identify biomarkers and the best diagnostic tests to detect such biomarkers to help identify the most likely effective treatment combinations.

DIGITAL HEALTH TECHNOLOGIES

U.S. health care is on the brink of a new revolution with the infusion of novel software and hardware technologies, referred to as digital health technologies, that aim to advance care management and delivery. Digital health technologies promise to improve patient outcomes through enhanced data collection and information flow. While some of these tools such as electronic health records have already become a new standard for patient care, others are just being introduced into clinical research and practice. These include connected devices that enable remote health monitoring (Internet of Things), wearables and activity trackers, smartphone apps, electronic patient-reported outcomes, telehealth and telemedicine, and digital therapeutics, among others. Digital health technologies have the potential to impact the full spectrum of clinical cancer care, from prevention and screening to treatment management, posttreatment follow-up, and survivorship. Effective implementation of these technologies may reduce health care costs and workflow inefficiencies and improve overall health care value, patient outcomes, and quality of life (335) (336).

One application of digital health has been effective collection and integration of patient-reported outcomes (PROs) into clinical care. PROs enable direct measurement of the experiences of patients with cancer that until recently have primarily been captured when patients fill out questionnaires to report symptoms (337). However, innovative methods to document PROs, captured through wearable devices or mobile apps on smartphones, are increasingly providing a critical new perspective in 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 and clinicians with a vast amount of previously untapped 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 clinical trial designs. In fact, several recent clinical trials have demonstrated that remote monitoring via digital heath platforms can reduce symptoms and improve survival (272) (338). Ongoing efforts are investigating the value of digital health technologies in enhancing efficiency in clinical trials, reducing barriers that give rise to cancer health disparities, promoting healthy behavior among cancer survivors, and evaluating new models of care delivery, such as home-based cancer treatments, among other endeavors.

ONGOING DEVELOPMENTS IN RADIATION THERAPY

Radiation therapy represents one of the central pillars of cancer treatment (see **Figure 10,** p 60). It has vital roles in curative and palliative treatment of patients with many types of cancer. Numerous new approaches are currently being studied to further improve the effectiveness of radiotherapy. One of the most promising new approaches is "FLASH" radiotherapy (FLASH-RT) (339). FLASH-RT involves delivering an extremely high dose of radiation in a very short period of time (340). It requires powerful devices capable of producing a radiation flow rate that is a thousand times more intense than that of conventional radiotherapy. Traditionally, radiation is delivered at a dose rate of approximately 0.03 Gray per second while FLASH-RT uses an ultrahigh dose-rate of 300 Gray per second. Consequently, radiation is delivered into the tumor in less than 200 milliseconds, compared to several minutes with standard radiotherapy. According to preliminary reports, a major advantage of FLASH-RT is that healthy tissue seems to better withstand this new method of radiotherapy, while the tumor has the same level of sensitivity to FLASH-RT as to conventional radiation (341).

Researchers are experimenting with a range of different ideas using FLASH-RT. One area of interest is evaluating whether FLASH-RT might benefit pediatric patients with brain tumors; the idea being tested is whether it could be used to reduce side effects in patients with standard risks, to increase the dose in patients with the most aggressive tumors, and to treat the very youngest patients who are most vulnerable to the long-term risk of side effects. In parallel with efforts to evaluate FLASH-RT in clinical care, basic scientists are also trying to gain a better understanding of why healthy tissue has a higher tolerance to this form of radiation.

COMBATTING CANCER THROUGH SCIENCE-BASED, PATIENT-CENTERED POLICIES

IN THIS SECTION, YOU WILL LEARN:

- Federal funding for medical 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 the progress against cancer.
- Policies and federally funded public health programs, many of which are supported by the CDC, ensure that individuals have access to preventive services, screening, and coverage for cancer treatment.
- Tobacco control policies improve public health and reduce cancer risk.
- Newly passed legislation aims to improve outcomes for children and adolescents who are diagnosed with cancer.

There has never been a time of greater promise in cancer research. As highlighted throughout this report, the rapid pace of progress and the broadening scope of the advances made in recent years have been extraordinary. Moreover, there has been an exceptionally strong and sustained commitment from our nation's policy makers, in particular, Senator Roy Blunt (R-MO), Senator Patty Murray (D-Wa), Congressman Tom Cole (R-OK), and Congresswoman Rosa DeLauro (D-CT), for supporting medical research including cancer research. In their respective roles on the Labor-Health and Human Services (HHS)-Education Appropriations Subcommittees in the Senate and House, these four champions of medical research have been instrumental in securing four consecutive years of robust annual funding increases for the NIH. As a result of these increases, the NIH budget has increased by 30 percent from FY 2015 to FY 2019.

This positive momentum for robust annual funding increases for the NIH signals an awareness among members of Congress of the critical role that NIH-funded research plays in preventing, detecting, diagnosing, and treating cancer and other diseases. For research investments to yield dividends in the form of new medical products and community-based programs that improve public health, strong federal investments are also needed in the FDA and CDC, and in evidence-based policy making across and throughout the medical research ecosystem (see sidebar on **Overcoming Cancer through Science Policy,** p. 112).

SUSTAINING THE MOMENTUM WITH ROBUST ANNUAL FUNDING INCREASES FOR MEDICAL RESEARCH

Federal funding through the NIH is the engine that drives medical research in the United States. It forms the foundation upon which many scientific discoveries are made and many life-changing treatments are developed. In fact, many of the major medical breakthroughs made in the last five decades, including much of the extraordinary progress detailed in this report, can be traced in part back to NIH research grants(28).

The accelerated pace and scope of the progress being made in cancer science and medicine would not have been possible without strong bipartisan leadership in the U.S. House and

OVERCOMING CANCER THROUGH SCIENCE POLICY

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

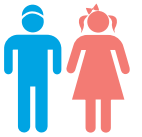
Sustain annual increases in federal funding for biomedical research, including support for a vibrant research workforce.

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.



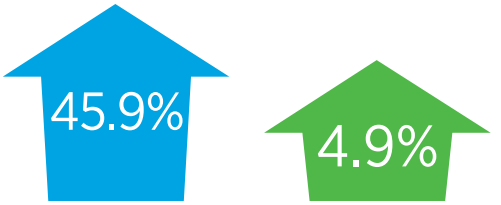
Senate, which has made medical research a national priority in recent years and has set the budgets for the NIH and NCI on a path of annual growth above inflation (see **Figure 16,** p. 113). Since FY 2015, Congress has renewed its commitment to the promise of medical research and increased the NIH budget by a total of $9 billion over the past 4 years. With this growth, the troubling trend of stagnant budgets that persisted for more than a decade prior to 2015 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. The National Cancer Moonshot Initiative is designed to further accelerate the pace of progress in specific priority areas at the NCI where researchers are poised to make great strides in the coming years (see sidebar on **the National Cancer Moonshot Initiative,** p. 116).

While this strong commitment to funding medical research has resulted in enormous accomplishments throughout the multidisciplinary field of cancer research, particularly in the area of precision medicine, a concerning trend is taking place. Specifically, there is a falling payline, and the success rate for the funding of investigator-initiated research project grants (RPGs) at the NCI has been declining. This may be attributable to the fact that the remarkable advances in and enthusiasm for cancer research have stimulated an unprecedented 50 percent increase in the number of investigator-initiated RPG applications to the NCI since FY 2013.

This dramatic increase in investigator-initiated RPG applications is unique to the NCI compared with other NIH institutes, where the number of applications has remained relatively constant during this same period. Given that NCI's budget has not increased at the same rate as its investigator-initiated RPG applications, the payline for these awards in 2018 was only 8 percent of approved grants, and the success rate was 11.3 percent. This means that a disproportionate and increasing number of exceptional applications (that is, those in the 11–15 percent scoring range) are not being funded at the NCI. If current trends persist or worsen, they will create a significant disincentive for investigators at all stages of their careers to submit grant applications to the NCI and even to remain in cancer research. This will have a stifling effect on cancer research at a time when impactful new discoveries are occurring at an ever-increasing pace and are having a beneficial impact on reducing cancer incidence and mortality rates.

As noted by **Senator Richard Shelby** (see p. 114) medical research is one of the most important investments that our

FROM 2013 TO 2018, R01 APPLICATIONS INCREASED BY:



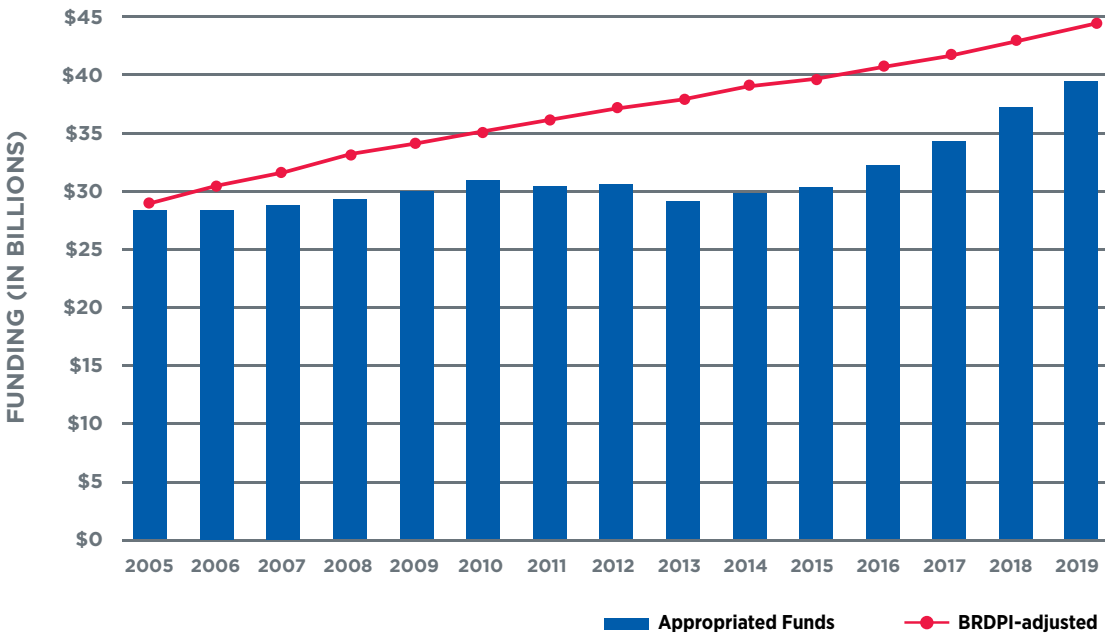
At the National Cancer Institute (NCI)

At the other 26 institutes and centers of the National Institutes of Health (NIH)

Data from NIH RePORTER

FIGURE 16

NIH FUNDING: BUILDING ON FOUR STRAIGHT YEARS OF ROBUST INCREASES



Four consecutive years of robust increases have provided positive momentum that will drive progress in the future. The biomedical research and development price index (BRDPI) reflects the rising cost of personnel, supplies, and equipment needed to conduct medical 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 4 consecutive years of significant funding increases, which have resulted in an overall 30 percent increase in funding since fiscal year (FY) 2015 and narrowed the gap between BRDPI levels and appropriated funds during this particular time period.

government can make, and the impact is felt in every part of the country. In fact, of the funds appropriated by Congress to the NIH, the vast majority (nearly 85 percent) is awarded to scientists in all 50 states and the District of Columbia through a competitive review process. The impact of federal support for the NIH and NCI also reaches well beyond the laboratory and the clinic. As the largest single public funder of medical research in the world, NIH-funded research throughout the country generated more than $74 billion in U.S. economic activity last year alone and supported more than 430,000 jobs (342).

The significant NIH funding increases of the last 4 years have been critical in returning medical research funding to a trajectory of steady growth. However, with so many opportunities for further advances against cancer and other diseases, it is vital that our elected officials take the steps necessary to ensure that this momentum for robust and sustained annual funding increases continues in the future (see **The AACR Call to Action,** p. 124).

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. The cancer workforce of tomorrow also must reflect the increasing diversity in our country, including disciplinary, gender, racial, ethnic, and geographic diversity.

"...I WILL CONTINUE MAKING NIH AND CANCER RESEARCH FUNDING A PRIORITY."

THE HONORABLE

RICHARD SHELBY

AGE 85 | U.S. SENATOR FOR ALABAMA

CHAMPIONING POLICIES AND LEGISLATION THAT PROMOTE MEDICAL BREAKTHROUGHS

I am a prostate cancer survivor and have been cancer-free for 24½ years. The cancer diagnosis changed my perspective on life. It made me appreciate every day. I get up in the morning and am eager to get to work. I do my best to support policies and legislation that will reinforce and promote impactful discoveries in the medical field, particularly as they pertain to research and curing terminal diseases such as cancer.

In 1994, I was diagnosed with prostate cancer after a prostate-specific antigen (PSA) test indicated that I had elevated PSA levels and needed follow-up. My doctors at the Walter Reed Army Hospital offered me several treatment options, and I opted to have surgery. I am immensely grateful for my doctors; they saved my life. I also know that if it weren't for the advancements in research that provided me with cutting-edge treatment options I might not be here today.

I am not the only member of my family who has had cancer. Several family members have been diagnosed with the disease, and my father passed away from prostate cancer when he was 77. Cancer has been prevalent in my life, and it has motivated me to do everything in my power to support revolutionary breakthroughs in cancer research and advancements in medicine.

A balance in public and private funding for medical research is important. Several companies in the private sector do a great job of researching and discovering new medications for dozens of diseases that affect Americans. However, private research dollars do not reach every form of cancer and rare disease. Therefore, funding for government agencies such as the National Institutes of Health (NIH) is paramount.

I am extremely proud of the fact that since I joined the Senate Appropriations Committee in 1994, we have nearly quadrupled medical research funding for NIH. In FY 2019, we appropriated more than $39 billion for this vital government agency, and each year we closely analyze what this important funding amount should be.

Increasing funding for NIH and other medical research institutions not only benefits patients, it also brings high-paying research jobs to colleges and universities across the country. This boost in medical research job opportunities aids statewide economies and local communities.

In Alabama, our research institutions received more than $350 million last year in medical research grants from NIH, and I am proud to know that a researcher in Alabama may be able to find the next breakthrough in cancer treatment or advance against another disease such as lupus. In fact, the University of Alabama at Birmingham is one of the leading research hospitals focusing on advancements in precision medicine—the next generation of health care, discovery, and innovation. Additionally, the Mitchell Cancer Institute at the University of South Alabama in Mobile treats thousands of cancer patients each year and hosts cutting-edge research.

The United States leads the world in medical research. Our dedicated and hard-working researchers are continually making innovative discoveries and are poised to find new and lasting cures and treatments. Any reduction in government funding will hinder these efforts moving forward.

That is why I will continue making NIH and cancer research funding a priority. It gives hope to families battling cancer and helps more people live longer, healthier lives.

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.

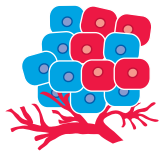
The 21st Century Cures Act, passed in 2016, authorized $1.8 billion over 7 years to fund the Cancer Moonshot. The same year, NCI convened a Blue Ribbon Panel (BRP) of many of the nation's top cancer experts to provide recommendations to the National Cancer Advisory Board on what could be done to expedite progress against cancer.

Based on collaborations with colleagues from across the cancer research community, the BRP made recommendations in 10 areas of cancer research that could accelerate progress across the entire cancer continuum and help meet the goals of the Cancer Moonshot. These opportunities were made possible by decades of investment in basic science and sustained support for the entire cancer research enterprise.

To date, Congress has appropriated $1 billion, with which the NCI has launched a series of new scientific programs that directly address each of the recommendations of the BRP. These programs provide the research community with new resources to pursue critical research questions and to build collaborations to ensure their success. Examples of new and ongoing Cancer Moonshot projects include:

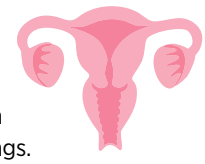
Facilitating the discovery and development of cellular immunotherapies for patients with cancer.

Studying the interaction between pancreatic tumors and the microenvironment to inform the design of new immunotherapies.



Improving smoking cessation treatment at NCI-designated cancer centers through implementation science.

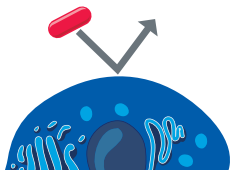
Determining the effectiveness of novel cervical cancer screening methods and identifying effective cervical cancer control strategies in both high- and low- resource settings.



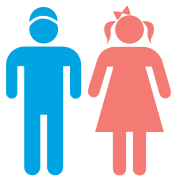
Supporting new multidisciplinary collaborative projects that bring together complementary technology platforms and approaches to enhance their capabilities for studies of cancer.

Developing dynamic 3D human tumor atlases to help inform cancer treatment and prevention options for cancer patients.

Developing new experimental models for studying drug resistance in tumors and designing innovative approaches to enhance the sensitivity of cancer cells to specific treatments.



Advancing immunotherapies for high-risk pediatric cancers and developing new treatments for pediatric cancers driven by fusion oncoproteins which are critical drivers of many childhood cancers.



NCI is currently planning new research opportunities for FY 2020 and beyond.
For more information and updates, visit: cancer.gov/moonshot

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 a critical 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 the new policies enacted through the NIH Office of Extramural Research, including the Next Generation Research Initiative. This special program is focused on ensuring the long-term stability and strength of the U.S. medical research enterprise by supporting early-stage investigators and mid-career investigators through specific funding efforts.

The NCI has also implemented innovative programs to support early-career investigators. For example, in January 2018, the NCI announced the establishment of the Method to Extend Research in Time (MERIT) (R37) Award, which is a grant that provides longer term support to early-career investigators. Eligible investigators may obtain up to 7 years of support in two segments: an initial 5-year award and an opportunity for an extension of up to two additional years, based on an expedited NCI review of the accomplishments during the initial funding segment. By providing an opportunity for longer term support, the NCI hopes to provide these individuals with more opportunities to take creative risks in their research projects and allow them to have additional time to successfully establish their careers before having to submit renewal applications.

ADVANCING REGULATORY SCIENCE AND POLICY

As the pace of innovation accelerates and our armamentarium against cancer expands, the FDA must be equipped to review an ever-increasing number of advances. Therefore, it is vital that the agency also receive consistent, robust support from Congress through the annual appropriations process. Appropriated dollars support critical regulatory science initiatives that foster the development of evidence-based regulatory policies that promote cutting-edge scientific advancement and expedited approval of medical products.

Authorized by the 21st Century Cures Act, the Oncology Center of Excellence (OCE) was established in 2017 to streamline the review of anticancer therapeutics and increase regulatory efficiency by bringing together staff with oncology expertise from the medical product centers of the FDA—the Center for Drug Evaluation and Research (CDER), the Center for Biologics Evaluation and Research (CBER), and the Center for Devices and Radiological Health (CDRH). In 2018, the OCE approved 19 new anticancer therapeutics.

In addition to coordinating the reviews of anticancer therapeutics, the OCE is focused on regulatory innovation. For example, the OCE began two pilot programs known as Real-Time Oncology Review (RTOR) and Assessment Aid to accelerate review timelines for anticancer therapeutics (see sidebar on **Pilot Programs Showcase Regulatory Innovation,** p. 118). RTOR and Assessment Aid have already paid dividends, initially for expanding the uses of previously approved anticancer therapeutics, but in May 2019, the FDA used these programs when it approved the new molecularly targeted therapeutic alpelisib for treating certain patients with breast cancer (see **Providing New Options for Patients with Breast Cancer,** p. 72).

In 2019, the OCE launched two exciting regulatory science and policy initiatives, Project Renewal and Project Facilitate. Project Renewal is a critical public health initiative designed to update safety and efficacy information on outdated product labels of long-standing, generic anticancer therapeutics. Currently, physicians may not be able to depend on the prescribing information described in the out-of-date labels of generic drugs such as 5-fluorouracil, and this causes health care providers to seek information from other sources and increases risk to patients. Working together with the cancer research community, the OCE is seeking to transform outdated generic product labels for 40 generic drugs into living documents with clearly established processes for updating the information. Under Project Facilitate, the OCE established a "one-stop shop" call center at the FDA to serve and support physicians seeking to use the agency's Expanded Access Programs for oncology patients (see sidebar on **Facilitating Patient Access to Promising Investigational Drugs (Project Facilitate),** p. 119).

The FDA is building on advances in technology to incorporate real-world data (RWD) and real-world evidence (RWE) into its processes for approving treatments, expanding drug labels, and monitoring therapies currently on the market. RWD can come from a variety of sources, including medical claims data, electronic health records, patient-reported outcomes, and product or disease registry data. RWE is clinical evidence generated from these data. Leveraging RWE for regulatory purposes continues to increase as policy mandates, established by the 21st Century Cures Act and other legislation, accelerate efforts to characterize regulatory-grade real-world evidence and develop methodologies to support its use. The "Framework for FDA's Real-World Evidence Program," which the agency released at the end of 2018, described their multifaceted approach to identify and use RWE to support regulatory decisions regarding the effectiveness of drugs, devices, and biologics. Demonstration projects, stakeholder engagement, and establishing internal processes for evidence evaluation will be vital to the program's success.

PILOT PROGRAMS SHOWCASE REGULATORY INNOVATION

Begun in 2018, the Real-Time Oncology Review (RTOR) and Assessment Aid (AA) pilot programs share the goal of improving the efficiency of the U.S. Food and Drug Administration (FDA) review process and speeding the delivery of safe and effective drugs and biologics to cancer patients.

RTOR:

- Allows the FDA to access key datasets before the official submission of a new drug or biologic license application.
- With earlier access to data, the FDA can begin reviewing the data earlier and communicate with the company before the formal submission.
- RTOR can drastically cut review time, typically to a few weeks after complete submission.

AA:

- AA is a template for a form that accompanies submission of a drug or biologic application in which most sections are divided into two parts: one to convey the company's position and one for the FDA's assessment.
- The goals of AA are to allow FDA reviewers to better focus on key details of an application, and to increase review efficiency through consistent formatting.

ADVANCING EFFECTIVE CANCER PREVENTION, TREATMENT, AND CONTROL EFFORTS

To maximize societal benefit from investments in medical research and the development of innovative medical products and technologies, the advances made must reach individuals, families, and communities through clinical care and public health programs. Public policies play a role in supporting equitable access to care and the delivery of effective public health programs such as screening, treatment, and vaccination programs (see sidebar on **CDC Cancer Prevention and Control Programs,** p. 120).

Through advances in research for the prevention, diagnosis, and treatment of cancers caused by the human papillomavirus (HPV) (see **Prevent and Eliminate Infection with Cancer-causing Pathogens,** p. 35), the elimination of cervical cancer and other HPV-related cancers is now an ambitious but feasible goal. According to experts, expanding the use of existing medical products and technologies could lead to the global elimination of HPV-related cancers as a public health problem within the century (127).

Unfortunately, the most effective prevention tool, the HPV vaccine, is underutilized in the United States. HPV vaccination rates in U.S. adolescents have risen in recent years, but thus far are only about half of the national 80 percent goal set by the U.S. Department of Health and Human Services in Healthy People 2020 (52). In November 2018, the President's Cancer Panel recommended several actions by policy makers and health care stakeholders to increase HPV vaccination rates to at least 80 percent of eligible recipients, including ensuring that providers are recommending HPV vaccine to all eligible adolescents and young adults during provider visits, promoting evidence-based communication campaigns to increase parents' acceptance of HPV vaccination, and encouraging continued health insurance coverage of HPV vaccine for eligible populations (120). In addition to HPV vaccination, cervical cancer screening and treatment for women who screen positive are needed to reduce and eventually eliminate cervical cancer. As of 2016, only 80 percent of eligible women were screened as recommended for cervical cancer, far below the Healthy People 2020 goal of 93 percent of eligible women screened. Continued funding for screening programs such as CDC's National Breast and Cervical Cancer Early Detection Program is essential for reaching the national screening goals. The elimination of HPV-related cancers in the U.S. will only be possible through concerted efforts by policy makers and stakeholders to increase vaccination rates and to improve screening and treatment of HPV-related cancer cases.

FACILITATING PATIENT ACCESS TO PROMISING INVESTIGATIONAL DRUGS (PROJECT FACILITATE)

The U.S. Food and Drug Administration (FDA) has helped provide access to investigational drugs for patients with few or no treatment options through its Expanded Access (EA) program since the 1980s. Between 2011 and 2016, the FDA received about 9,000 EA, or compassionate use, requests and approved 99 percent of them.

Launched in June 2019, Project Facilitate is a pilot project through which the FDA is seeking to streamline and increase access to investigational anticancer therapeutics. Through Project Facilitate, the FDA established a single point of contact, a call center, through which physicians can initiate and/or get help completing single-patient investigational new drug (SPI) requests. SPI requests are the way in which physicians secure the FDA's approval to treat individual patients with unapproved investigational therapeutics. Trained FDA staff will guide callers through the request process, assisting with the necessary paperwork and identifying contacts at pharmaceutical companies and institutional review boards (IRBs).

Because Project Facilitate staff will be copied on all requests to the companies, the FDA will, for the first time, be able to collect data on demand for and outcomes from the use of investigational (unapproved) anticancer therapeutics. Currently, the FDA only becomes aware of expanded access requests if they are accepted by the companies who developed the treatment. Companies will still be able to decide whether to provide requested therapeutics, but for requests initiated through Project Facilitate, they will be required to provide the rationale for denying access. Project Facilitate staff will follow up with physicians whose patients received investigational therapeutics to learn about how the patients did with the treatment.

Project Facilitate and Expanded Access operate in the same space as, but separate from, federal Right-to-Try legislation that was signed into law in 2018. Like Project Facilitate and EA, Right-to-Try is a mechanism by which terminally ill patients can request access to investigational therapeutics. However, unlike the FDA programs, the federal law circumvents involvement by the FDA and IRBs.

Globally, 630,000 people develop HPV-related cancers each year, and the vast majority—530,000—are cases of cervical cancer (343). In January 2019, at the World Health Organization (WHO) Executive Board meeting, the U.S. government was one of several countries that requested the development of a WHO global strategy to accelerate cervical cancer elimination, centering on improved HPV vaccine coverage, screening and treatment of cervical precancer, and treatment of invasive cancers. The global public health strategy is being created through a consultative process and will be presented for approval by member states at the 2020 World Health Assembly. The global targets under consideration for 2030 include: achieving 90 percent coverage of HPV vaccination for eligible populations, achieving 70 percent screening of eligible women for cervical cancer, and achieving 90 percent treatment of women identified with precancers and invasive cancers. In low- and middle-income countries, achieving these targets will include financing of HPV vaccination by organizations, such as the Gavi, the Vaccine Alliance, the development and market availability of HPV tests and other screening tests, and optimizing service delivery to ensure that women who screen positive are provided prompt treatment.

Ongoing efforts from scientific communities working together with members of Congress, NIH, CDC, and other

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 helped low-income, uninsured, and underinsured women gain access to screening, diagnostic, and treatment services. In 2017, the program provided breast cancer screening to nearly 286,000 women, diagnosing about 2,500 invasive breast cancers and 765 premalignant lesions before they turned into cancer. The program also provided cervical cancer screening to nearly 139,000 women, diagnosing around 170 invasive cancers and 6,000 premalignant lesions.

The Colorectal Cancer Control Program was established in 2015 to increase colorectal cancer screening rates. It currently includes 541 clinics that serve nearly 1 million patients ages 50 to 75, including many uninsured patients. Clinics that have participated since the program's inception have increased screening rates by 8.3 percent.

Since 1998, the National Comprehensive Cancer Control Program has provided funding and technical advice to all 50 states, the District of Columbia, seven U.S. Associated Pacific Islands and Territories, and eight tribes and tribal organizations to help them design and implement cancer control plans. The program focuses on issues such as prevention, early detection and treatment, survivorship, and health disparities.

The National Program of Cancer Registries (NPCR) supports 46 states, the District of Columbia, Puerto Rico, the U.S. Pacific Island Jurisdictions, and the U.S. Virgin Islands, to collect data on cancer occurrence, type of treatment, and outcomes. NPCR cancer registries collect and process more than 1.7 million new cancer cases annually.

The Cancer Prevention and Control Research Network is a network of academic, public health, and community partners who conduct community-based cancer research. A collaboration between CDC and NCI, the network aims to reduce the burden of cancer particularly among those who are disproportionately affected.

For more information, see cdc.gov/cancer.

federal agencies are needed to support and accelerate the elimination of HPV-related cancers in the U.S. and globally through public policy.

Despite advances in cancer research and care, there are persistent disparities in health outcomes for certain segments of the U.S. population, including racial and ethnic minorities, individuals of low socioeconomic status, and residents of rural areas (see sidebars **Which U.S. Population Groups Experience Cancer Health Disparities?** and **U.S. Cancer Health Disparities,** p. 13 and p. 14). Many drivers of cancer health disparities have been identified, and policy solutions are needed to help achieve health equity. One major issue is that many populations are underrepresented in clinical trials for developing new anticancer therapeutics. Barriers to patient participation in clinical trials that need to be addressed include financial barriers, restrictive eligibility criteria, and lack of information about and access to clinical trials.

Public policies are also needed to support continued innovation and greater access to treatment and diagnostic options for all cancer patients. The Centers for Medicare

and Medicaid Services (CMS) recently issued a National Coverage Determination (NCD) for CAR T-cell therapy, a novel, revolutionary therapy for certain patients with blood cancer (see **Treatment with Immunotherapy,** p.84). CMS will cover CAR T-cell therapies that are administered for FDA-approved indications and off-label use that is approved by CMS. While the coverage policy does not change how much CMS reimburses for CAR-T treatments, it is a helpful step toward ensuring that patients have access to innovative treatments as they are developed and approved.

In March 2018, CMS announced their decision on national Medicare coverage for next-generation sequencing (NGS) diagnostic tests for advanced cancers. At the time, CMS stated they would provide coverage for FDA-approved or-cleared companion in vitro diagnostic tests that specify treatment options for patients with recurrent, relapsed, refractory, metastatic, or advanced stage III or IV cancer that has not been tested previously with the same NGS test or for repeat testing using the same test when a new primary cancer diagnosis is made by the treating physician. Though the scope of the coverage decision was broader than initially proposed in earlier drafts, repeat NGS testing for some primary cancers and germline hereditary testing did not receive coverage from CMS. In April 2019, CMS reopened the NCD for such NGS tests for advanced cancers to specifically seek comment from the public on coverage for germline hereditary tests. CMS should carefully consider stakeholder feedback on these and future cancer technologies with the explicit goal to set coverage policy that supports continued innovation and ensures patient access to safe, effective, and clinically useful cancer treatments.

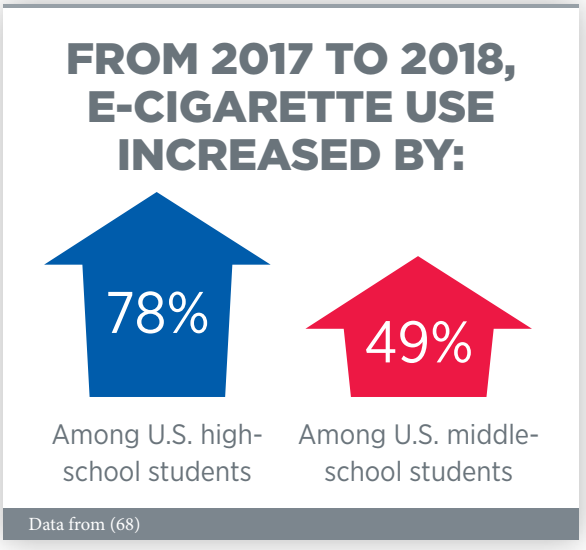
SUPPORTING PUBLIC HEALTH POLICIES TO REDUCE THE USE OF TOBACCO PRODUCTS

E-cigarettes, which first hit the U.S. market more than a decade ago, have grown in popularity during the past few years, despite little research on their long-term health effects. Most concerning is the fact that e-cigarettes are now the most commonly used tobacco product among U.S. youth and young adults. According to the 2018 National Youth Tobacco Survey (NYTS), a nationally representative survey funded by FDA and CDC, current e-cigarette use—or "vaping"—among middle and high school students increased alarmingly between 2017 and 2018, with over 3.6 million kids using e-cigarettes in 2018. Among high-school students, e-cigarette use jumped 78 percent from 2017 to 2018. This is especially concerning because we know that youth who use e-cigarettes are more likely to try combustible cigarettes later (66).

The authors of the NYTS study hypothesized that last year's increase in e-cigarette use among youth and young adults could be attributable to use of USB flash drive-like e-cigarettes, such as JUUL, which have garnered substantial popularity. These products have very high nicotine content; appealing flavors; and the ability to be easily concealed and used discreetly.

In response to these alarming data, many public health experts believe that youth e-cigarette use has reached an epidemic proportion. In September 2018, the FDA launched massive enforcement actions against retailers for selling e-cigarettes to minors. In addition, the FDA announced plans to limit most e-cigarette sales to age-restricted, in-person locations and to heighten age-verification measures for online sales to try to ensure that minors are not able to buy popular flavored e-cigarette pods. Additionally, on December 18, 2018, the U.S. Surgeon General issued an advisory on youth e-cigarette use, urging parents, teachers, health professionals, and government officials to take "aggressive steps" to keep children from using e-cigarettes (65). He also called for new local restrictions, including increased taxes on electronic nicotine products and indoor e-cigarette use bans.

The rise of e-cigarette use puts the United States at risk of losing the progress that has been made against smoking in the last 30 years. Over the past three decades, the smoking rate among U.S. adults has fallen almost 12 percentage points (from 25.5 percent in 1990 to 14 percent in 2017) and, with tobacco use as the leading cause of preventable death, we cannot afford to lose the tremendous progress that has been made in curbing tobacco use (18) (344). Therefore,



THE HONORABLE
DICK DURBIN

U.S. SENATOR FROM ILLINOIS

"We waited too long to protect people from the harm of cigarettes, and there were many victims, including my father—at the age of 53 he died of lung cancer. We're making the same mistake today with e-cigarettes."

the strategies that worked to reduce the rates of combustible cigarette use, which included increasing the price, warning the public of the risks, and prohibiting flavors, may need to be applied to e-cigarettes, especially since these are proven evidence-based measures that have resulted in a reduction of tobacco products by youth in the past.

While additional research is needed to fully understand the short- and long-term harms of e-cigarette use, it is very clear that these products have no place in the hands of youth or young adults. An additional challenge that we are facing today involves the fact that youth and young adults often have a misconception that e-cigarettes are safe. This misconception must be corrected, especially when considering that there is now an expanded group of youth who are at risk of a lifetime addiction to nicotine products. This has prompted the FDA to begin a youth prevention campaign (The Real Cost) to help increase awareness among young people of the health risks of e-cigarettes.

The AACR, along with other public health groups, strongly supports prohibiting the sale of tobacco products to individuals under the age of 21. Nearly all tobacco use begins in youth and young adulthood, and 95 percent of adult smokers begin smoking before they turn 21. However, we also recognize that this is one among several important federal policy changes needed to address the public health crisis of e-cigarette use among U.S. youth and young adults. Other potential actions include prohibiting the manufacture and sale of all flavored tobacco products (unless they are FDA-approved to aid in tobacco cessation); restricting online sale of all tobacco products, particularly to underage purchasers; strongly supporting the actions that the Center for Tobacco Products at the FDA is taking to regulate the manufacturing, distribution, and marketing of tobacco products; and increasing funding of the prevention and cessation activities of the CDC Office on Smoking and Health.

PROMOTING POLICIES TO FURTHER OUR PROGRESS AGAINST PEDIATRIC CANCER

Cancer remains the second leading cause of death among U.S. children ages 1–14 (345). In the last few years, important strides have been made to further progress against pediatric cancers through the passage and implementation of two important pieces of legislation and programs at the NCI (see sidebar on **the NCI Childhood Cancer Data Initiative,** p. 123).

On August 18, 2017, key provisions of the Research to Accelerate Cures and Equity (RACE) for Children Act were signed into law as part of the FDA Reauthorization Act of 2017. Under these provisions, the FDA may require companies developing targeted cancer drugs for adults to develop those drugs for children with cancer as well. This is an important policy change, because the relatively small population of children with cancer provides little market incentive for the biopharmaceutical industry to develop new pediatric oncology drugs.

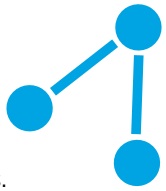
The RACE Act provisions are an update to the Pediatric Research Equity Act (PREA) of 2003. Under PREA, drug companies were required to develop drugs to treat diseases for children as well as adults. This was not applied to cancer, however, because cancers develop in different organs in children and adults. Under the new law, companies developing a cancer treatment for adults would also undertake PREA studies in children when the molecular target of the drug is relevant to a pediatric cancer.

As required by the RACE Act provisions, the FDA has developed a Pediatric Molecular Target List to provide guidance to industry in planning for new drug and biologic

NCI CHILDHOOD CANCER DATA INITIATIVE

In March 2019, the NCI announced the Childhood Cancer Data Initiative (CCDI), which focuses on the development of a framework to "collect, analyze, and share data to address the burden of cancer in children, adolescents, and young adults." Data-sharing is especially critical for tackling pediatric cancers because they are rare, affecting a total of 16,000 patients a year in the United States.

The database would integrate multiple types of data, including genomics, proteomics, imaging, pathology, and clinical data including side effects and patient and caregiver reported outcomes.



Privacy and ethical issues regarding data-sharing will also need to be addressed as governance frameworks are developed.

The FDA's "The Real Cost" youth e-cigarette prevention campaign focuses on educating the nearly 10.7 million youth ages 12-17 who have ever used or are at risk of using e-cigarettes on their potential dangers, such as nicotine addiction and exposure to other chemicals. Campaign ads can be found in schools, on television, and on digital and social media sites where teens spend most of their time.

submissions. The list includes molecular targets that have potential relevance to the growth or progression of at least one type of pediatric cancer and those molecular targets for which there is no evidence of association with the growth or progression of pediatric tumors and will be updated as new evidence becomes available. The requirement for companies to assess the potential use of new therapies for pediatric as well as adult cancer patients will go into effect on August 18, 2020.

In May 2018, Congress passed the Childhood Cancer Survivorship, Treatment, Access, and Research (STAR) Act of 2018. 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. Specifically, the STAR Act:

- Increases opportunities for childhood cancer research by authorizing NCI to expand existing efforts to collect biospecimens for childhood cancer patients enrolled in NCI-sponsored clinical trials.
- Improves childhood cancer surveillance by authorizing grants to state cancer registries to identify and track incidences of child, adolescent, and young adult cancer.
- Enhances research on the late effects of childhood cancers to improve the lives of childhood cancer survivors.
- Ensures pediatric expertise at the NIH by requiring the inclusion of at least one pediatric oncologist on the National Cancer Advisory Board.

In January 2019, the NCI announced a request for applications (RFA) titled *Improving Outcomes for Pediatric, Adolescent and Young Adult Cancer Survivors.* This announcement builds on the NCI's ongoing commitment toward advancing cancer survivorship for these patients and directly aligns with STAR Act provisions for research that will help us better understand and meet the needs of childhood cancer survivors.

THE AACR CALL TO ACTION

Research is driving progress against cancer because it is the foundation of every lifesaving clinical advance and every new policy designed to improve the health of the nation. These remarkable advances are illustrated by the declining cancer death rate and the rising number of children and adults who survive a cancer diagnosis.

Much of the research that is fueling these advances is supported by federal investments in the NIH. Strong, bipartisan support in Congress has resulted in four consecutive years of robust funding increases for the NIH. 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.

The enthusiasm and support for medical research are more than justified because we have unprecedented scientific knowledge and capability to deliver more advances across the continuum of cancer care in the future.

THAT IS WHY THE AACR URGES CONGRESS TO:

- Continue to support robust, sustained, and predictable growth of the NIH budget by providing an increase of at least $2.5 billion for NIH in fiscal year (FY) 2020, for a total funding level of at least $41.6 billion.
- Ensure that the funding designated through the 21st Century Cures Act for targeted initiatives, including the National Cancer Moonshot, is fully appropriated in FY 2020 and is supplemental to the increase in the NIH base budget.
- Support the FDA's critical regulatory science initiatives by providing an increase of at least $316 million in discretionary budget authority for medical products.
- Support the CDC Cancer Prevention and Control Programs with total funding of at least $555 million. This includes funding for comprehensive cancer control, cancer registries, and screening and awareness programs for specific cancers.

By providing robust, sustained, and predictable annual funding increases for the NIH, coupled with consistent and sufficient funding for the FDA and the CDC in FY 2020 and beyond, Congress will continue to help us transform cancer care, increase survivorship, spur economic growth, and maintain the United States' position as the global leader in science and medical research. These vital investments will not only strengthen the U.S. research enterprise, but also 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 completed to lower the risk that the cancer will come back. Adjuvant therapy may include chemotherapy, radiotherapy, hormone therapy, targeted therapy, or immunotherapy.

Antibody–drug conjugate A therapeutic comprising an antibody chemically linked to a cytotoxic chemotherapeutic. The antibody binds to specific proteins on the surface of certain types of cells, including cancer cells. The linked cytotoxic chemotherapeutic enters these cells and kills them without harming nearby cells.

B cell A type of immune cell that makes proteins, called antibodies, which bind to microorganisms and other foreign substances, and help fight infections. A B cell is a type of white blood cell. Also called B lymphocyte.

Big data Data sets that are too large and complex for processing by traditional database management tools.

Biomarker A biological molecule found in blood or other body fluids or tissues that is a sign of a normal or abnormal process, or of a condition or disease. A biomarker may be used to see how well the body responds to a treatment for a disease or condition.

Biomedical 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.

Bladder cancer Cancer that forms in tissues of the bladder, the organ that stores urine. The most common type of bladder cancer is transitional cell carcinoma, also called urothelial carcinoma.

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.

Cancer A term for diseases in which abnormal cells divide without control and can invade nearby tissues. Cancer cells can also spread to other parts of the body through the blood and lymph systems. There are several main types of cancer. Carcinomas begin in the skin or in tissues that line or cover internal organs. Sarcomas begin in bone, cartilage, fat, muscle, blood vessels, or other connective or supportive tissue. Leukemias arise in blood-forming tissue, such as the bone marrow, and cause large numbers of abnormal blood cells to be produced and enter the blood. Lymphomas and multiple myeloma originate in the cells of the immune system. Central nervous system cancers arise in the tissues of the brain and spinal cord. Also called malignancy.

Carcinogen Any substance that causes cancer.

Cervical cancer Cancer that arises in the cervix (the area where the uterus connects to the vagina). The two main types of cervical cancer are squamous cell carcinoma and adenocarcinoma. Most cervical cancers are caused by persistent infection with certain strains of human papillomavirus (HPV). Normal cells of the cervix do not suddenly become cancerous; they first gradually develop precancerous changes, then later turn into cancer. These changes can be detected by the Papanicolaou (Pap) test and treated to prevent the development of cancer.

GLOSSARY

Chemotherapy The use of drugs to kill or slow the growth of cancer cells.

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.

Chronic lymphocytic leukemia (CLL) One of the most common types of leukemia (blood cancer) diagnosed among adults in the United States. CLL arises in lymphocytes, most commonly B lymphocytes, in the bone marrow, which then enter the blood. It is usually slow growing, but in some people, it can be fast growing.

Clinical trial A type of research study that tests how well new medical approaches work in people. These studies test new methods for screening, preventing, diagnosing, or treating a disease. Also called clinical study.

Colonoscopy Examination of the inside of the colon using a colonoscope that is inserted into the rectum. A colonoscope is a thin, tube-like instrument with a light and a lens for viewing. It may also have a tool to remove tissue to be checked under a microscope for signs of disease.

Colorectal cancer Cancer that forms in the colon or the rectum. More than 95 percent of colorectal cancers are adenocarcinomas that arise in cells forming glands that make mucus to lubricate the inside of the colon and rectum. Before a colorectal cancer develops, a growth of tissue or tumor usually begins as a noncancerous polyp on the inner lining of the colon or rectum. Polyps can be found—for example, through colonoscopy—and removed before they turn into cancer.

Computed tomography (CT) A series of detailed pictures of areas inside the body taken from different angles. The pictures are created by a computer linked to an X-ray machine. Also called CAT scan, computerized axial tomography scan, and computerized tomography.

Cutaneous squamous cell carcinoma Cancer that begins in cells that form the outer layer of the skin, epidermis.

Cytotoxic An agent or substance that is toxic to living cells.

Death rate/mortality rate The number of deaths in a certain group of people in a certain period of time. Death rates may be reported for people who have a certain disease; who live in one area of the country; or who are of a certain gender, age, or ethnic group.

Deoxyribonucleic acid (DNA) The molecules inside cells that carry genetic information and pass it from one generation to the next.

Electronic cigarette (e-cigarette) A battery-powered device that delivers nicotine by vaporizing a nicotine solution, rather than by combusting tobacco as do traditional cigarettes and cigars.

Epigenetic mark A chemical modification of DNA and/or histones that can control the accessibility of genes. The collection of epigenetic marks across the entire genome is referred to as the epigenome.

Epigenetics The study of heritable changes in gene expression or cellular phenotype caused by mechanisms other than changes in DNA sequence. Examples of such changes might be DNA methylation or histone deacetylation, both of which serve to suppress gene expression without altering the sequence of the silenced genes.

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.

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 and most genes contain the information for making a specific protein.

Hairy cell leukemia A rare form of leukemia in which abnormal B cells are present in the bone marrow, spleen, and peripheral blood.

Hepatocellular carcinoma (HCC) HCC is the most common type of liver cancer. It occurs mostly in people with chronic liver diseases, such as cirrhosis caused by infection with hepatitis B virus or hepatitis C virus.

HER2 A protein found on the surface of some cells that can initiate a variety of signaling pathways, causing the cells to proliferate. It is found at abnormally high levels on the surface of many types of cancer cells, including some breast cancer cells, so these cells may divide excessively. Also called ERBB2 and NEU.

Histone A type of protein found in chromosomes. Histones attach to DNA and help control which genes are accessible for reading.

Hodgkin lymphoma A cancer of the immune system that starts in white blood cells called lymphocytes.

Hormone One of many chemicals made by glands in the body. Hormones circulate in the bloodstream and control the actions of certain cells or organs. Some hormones can also be made in the laboratory.

Human papillomavirus (HPV) A type of virus that can cause abnormal tissue growth (e.g., warts) and other changes to cells. Infection for a long time with certain types of HPV can cause cervical cancer. HPV also plays a role in some other types of cancer, including anal, oropharyngeal, penile, vaginal, and vulvar cancers.

Immune system A diffuse, complex network of interacting cells, cell products, and cell-forming tissues that protects the body from invading microorganisms and other foreign substances, destroys infected and malignant cells, and removes cellular debris. The immune system includes the thymus, spleen, lymph nodes and lymph tissue, stem cells, white blood cells, antibodies, and lymphokines.

Immunotherapy Treatment designed to produce immunity to a disease or enhance the resistance of the immune system to an active disease process, such as cancer.

Incidence rate The number of new cases per population at risk in a given time period.

Leukemia Cancer that starts in blood-forming tissue, such as the bone marrow, and causes large numbers of blood cells to be produced and enter the bloodstream.

Liver cancer 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.

Mammogram An X-ray of the breast that is used to look for early signs of breast cancer.

Melanoma Cancer that begins in melanocytes (cells that make the pigment melanin). These cancers may arise in a mole (skin melanoma), but they can also originate in other pigmented tissues, such as the eye (uveal melanoma) or the intestines (mucosal melanoma).

Merkel cell carcinoma A rare type of cancer that forms on or just beneath the skin, usually in parts of the body that have been exposed to the sun. Also, called Merkel cell cancer, neuroendocrine carcinoma of the skin, and trabecular cancer.

Metastasis The spread of cancer from one part of the body to another. A tumor formed by cells that have spread is called a metastatic tumor or a metastasis. The metastatic tumor contains cells that are like those in the original (primary) tumor. The plural form of metastasis is metastases.

Molecularly targeted therapy A type of treatment that uses therapeutics to target specific molecules involved in the growth and spread of cancer cells.

Morbidity Refers to having a disease, a symptom of disease, the amount of disease within a population, or the medical problems caused by a treatment.

Mutation Any change in the DNA of a cell. Mutations may be caused by mistakes during cell proliferation or by exposure to DNA-damaging agents in the environment. Mutations can be harmful, beneficial, or have no effect. If they occur in cells that make eggs or sperm, they can be inherited; if mutations occur in other types of cells, they are not inherited. Certain mutations may lead to cancer or other diseases.

National Cancer Institute (NCI) The largest of the 27 institutes and centers of the National Institutes of Health. The NCI coordinates the National Cancer Program, which conducts and supports research, training, health information dissemination, and other programs with respect to the cause, diagnosis, prevention, and treatment of cancer; rehabilitation from cancer; and the continuing care of cancer patients and their families.

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.

GLOSSARY

Non–small cell lung cancer (NSCLC) A group of lung cancers that are named for the kinds of cells found in the cancer and how the cells look under a microscope. The three main types of NSCLC are squamous cell carcinoma, large cell carcinoma, and adenocarcinoma. NSCLC is the most common kind of lung cancer.

NTRK gene fusion A genetic alteration that occurs when a piece of the chromosome containing a gene called NTRK breaks off and joins with a different gene on another chromosome. NTRK gene fusions lead to abnormal proteins called TRK fusion proteins, which may cause cancer cells to grow. NTRK gene fusions are associated with many types of cancer, including cancers of the brain, head and neck, thyroid, soft tissue, lung, and colon. Also called neurotrophic tyrosine receptor kinase gene fusion.

Oncology The branch of medicine that focuses on cancer diagnosis and treatment.

Pathogen A bacterium, virus, or other microorganism that can cause disease. Also referred to as an infectious agent.

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 patients and their cancer.

Programmed death-1 (PD-1) A protein on the surface of immune cells called T cells. When PD-1 attaches to programmed death-ligand 1 (PD-L1) on other cells, it sends signals into the T cells to tell them to slow down and stop acting aggressively. Thus, PD-1 acts as an immune checkpoint protein or brake.

Programmed death-ligand 1 (PD-L1) A protein on the surface of many cell types, including some tumor cells. When it attaches to PD-1 on the surface of T cells, it sends signals into the T cells to tell them to slow down and stop acting aggressively.

Prostate cancer Cancer that starts in tissues of the prostate (a gland in the male reproductive system found below the bladder and in front of the rectum). In men, it is the most frequently diagnosed cancer and the second most common cause of death from cancer.

Prostate-specific antigen (PSA) A protein secreted by the prostate gland, increased levels of which are found in the blood of patients with cancer of the prostate.

Protein A molecule made up of amino acids that is needed for the body to function properly.

Psycho-oncology An interdisciplinary field to address the physical, psychological, social, and behavioral aspects of the cancer experience for both patients and caregivers.

Radiation Energy released in the form of particle or electromagnetic waves. Common sources of radiation include radon gas, cosmic rays from outer space, medical X-rays, and energy given off by a radioisotope (unstable form of a chemical element that releases radiation as it breaks down and becomes more stable).

Radiotherapy The use of high-energy radiation from X-rays, gamma rays, neutrons, protons, and other sources to kill cancer cells and shrink tumors. Radiation may come from a machine outside the body (external-beam radiation therapy), or it may come from radioactive material placed in the body near cancer cells (internal radiation therapy). Systemic radiotherapy uses a radioactive substance, such as a radiolabeled monoclonal antibody, that travels in the blood to tissues throughout the body. Also called irradiation and radiation therapy.

Receptor A protein in a cell that attaches to specific molecules, such as hormones, from outside the cell, in a lock-and-key manner, producing a specific effect on the cell—for example, initiating cell proliferation. Receptors are most commonly found spanning the membrane surrounding a cell but can be located within cells.

Renal cell carcinoma The most common type of kidney cancer. It begins in the lining of the renal tubules in the kidney. Also called hypernephroma, renal cell adenocarcinoma, and renal cell cancer.

Signaling pathway/signaling network A group of molecules in a cell that work together to control one or more cell functions, such as cell proliferation or cell death. After the first molecule in a pathway receives a signal, it alters the activity of another molecule. This process is repeated until the last molecule is activated and the cell function involved is carried out. Abnormal activation of signaling pathways can lead to cancer, and drugs are being developed to block these pathways. These drugs may help prevent cancer cell growth and kill cancer cells.

Small-cell lung cancer A fast-growing cancer that forms in tissues of the lung and can spread to other parts of the body. The cancer cells look small and oval-shaped when looked at under a microscope.

Standard of care The intervention or interventions generally provided for a certain type of patient, illness, or clinical circumstance. The intervention is typically supported by evidence and/or expert consensus as providing the best outcomes for the given circumstance.

Stereotactic body radiotherapy A type of radiation therapy that uses special equipment to position a patient and precisely deliver radiation to tumors in the body (except the brain). This type of radiation therapy helps spare normal tissue.

T cell A type of immune cell that protects the body from invading microorganisms and other foreign substances and that destroys infected and malignant cells. A T cell is a type of white blood cell. Also called T lymphocyte.

Treatment resistance The failure of cancer cells to respond to a treatment used to kill or weaken them. The cells may be resistant at the beginning of treatment or may become resistant after being exposed to the treatment.

Triple-negative breast cancer A type of breast cancer in which the cancer cells do not have estrogen receptors, progesterone receptors, or large amounts of HER2/neu protein. Also called ER-negative, PR-negative, HER2-negative breast cancer.

TRK proteins A family of proteins that are found on nerve cells. They are involved in cell signaling pathways that control cell growth, cell maturation, and cell survival. In some patients with cancer, the genes that make the TRK proteins, NTRKs, may have alterations that cause abnormal TRK proteins to be made. These abnormal proteins may be too active or found in higher than normal amounts on some types of cancer cells, which may cause cancer cells to grow. Also called tropomyosin receptor kinase protein family.

Tumor An abnormal mass of tissue that results when cells divide more than they should or do not die when they should. Tumors may be benign (not cancer) or malignant (cancer). Also called neoplasm.

Tumor microenvironment The cells, molecules, and blood vessels that surround and feed a cancer cell. A cancer can change its microenvironment, and the microenvironment can affect how a tumor grows and spreads.

*This list contains some of the specialized terms pertinent to the *AACR Cancer Progress Report 2019*.

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 liposome injection	Onivyde
brain tumors	lomustine	CeeNU
multiple cancers	mechlorethamine hydrochloride	Mustargen
multiple cancers	melphalan	Alkeran
certain lymphomas	methoxsalen	Uvadex
multiple cancers	mitoxantrone	Novantrone
colon cancer	oxaliplatin	Eloxatin
testicular cancer	plicamycin	Mithracin
certain lymphomas	procarbazine	Matulane
pancreatic cancer	streptozocin	Zanosar
melanoma; certain brain cancers	temozolomide	Temodar
certain leukemias	thioguanine	Thioguanine Tabloid
multiple cancers	thiotepa	Thioplex
ovarian and small cell lung cancers	topotecan	Hycamtin
colorectal cancer and stomach cancer	trifluridine and tipiracil	Lonsurf
bladder cancer	valrubicin	Valstar

INCREASING PRECISION

Cell Cytoskeleton–modifying Agents

Approved Indication	Generic Name	Trade Name
prostate cancer	cabazitaxel	Jevtana
multiple cancers	docetaxel	Taxotere
breast cancer; liposarcoma	eribulin mesylate	Halaven
breast cancer	ixabepilone	Ixempra
multiple cancers	paclitaxel	Taxol
breast, lung, and pancreatic cancers	paclitaxel albumin-bound particles	Abraxane
certain type of non-Hodgkin lymphoma	polatuzumab vedotin-piiq	Polivy
multiple cancers	vinblastine	Velban
certain leukemias and lymphomas	vincristine	Oncovin
certain leukemias and lymphomas	vincristine sulfate liposomes	Marqibo
breast and lung cancers	vinorelbine tartrate	Navelbine

* includes companion diagnostic

Some drugs are available in multiple formulations; these have only been listed once.

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

SUPPLEMENTAL TABLE 2 *(continued)*

FDA-APPROVED THERAPEUTICS FOR THE TREATMENT OF CANCER

Antinutrients

Approved Indication	Generic Name	Trade Name
certain leukemias	asparaginase	Elspar; Kidrolase
certain leukemias	calaspargase pegol-mknl	Asparlas

Gene Transcription Modifiers

Approved Indication	Generic Name	Trade Name
certain lymphomas	bexarotene	Targretin
liposarcoma and leiomyosarcoma	trabectedin	Yondelis
certain leukemias	tretinoin (all-trans retinoic acid)	Vesanoid

Radiation-emitting Drugs

Approved Indication	Generic Name	Trade Name
certain types of neuroendocrine tumors	iobenguane I 131	Azedra
certain types of neuroendocrine tumors	lutetium 177 dotatate	Lutathera
prostate cancer bone metastases	radium Ra 223 dichloride	Xofigo

Cell Death-promoting Agents

Approved Indication	Generic Name	Trade Name
certain form of leukemia	venetoclax	Venclexta

Hormones/Antihormones

Approved Indication	Generic Name	Trade Name
prostate cancer	abarelix	Plenaxis
prostate cancer	abiraterone acetate	Zytiga
breast cancer	anastrozole	Arimidex
prostate cancer	apalutamide	Erleada
prostate cancer	bicalutamide	Casodex
prostate cancer	darolutamide	Nubeqa
prostate cancer	degarelix	Firmagon
prostate cancer	enzalutamide	Xtandi
prostate cancer	estramustine	Emcyt; Estracyt
breast cancer	exemestane	Aromasin
prostate cancer	flutamide	Eulexin
metastatic breast cancer	fulvestrant	Faslodex
prostate and breast cancers	goserelin acetate implant	Zoladex
breast cancer	letrozole	Femara
prostate cancer	leuprolide acetate	Eligard; Lupron; Viadur
breast and endometrial cancers	megestrol acetate	Megace; Megace Oral Suspension
breast cancer	tamoxifen	Nolvadex
prostate cancer	triptorelin pamoate	Trelstar Depot

INCREASING PRECISION

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 mepesuccinate	Synribo

Nuclear Export Inhibitors

Approved Indication	Generic Name	Trade Name
multiple myeloma	selinexor	Xpovio

Epigenome-modifying Agents

Approved Indication	Generic Name	Trade Name
myelodysplastic syndrome	azacitidine	Vidaza
certain lymphomas	belinostat	Beleodaq
myelodysplastic syndrome	decitabine	Dacogen
certain type of leukemia	enasidenib*	Idhifa
certain type of leukemia	ivosidenib*	Tibsovo
multiple myeloma	panobinostat	Farydak
certain lymphomas	romidepsin	Istodax
certain lymphomas	vorinostat	Zolinza

* includes companion diagnostic

Some drugs are available in multiple formulations; these have only been listed once.

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

SUPPLEMENTAL TABLE 2 *(continued)*

FDA-APPROVED THERAPEUTICS FOR THE TREATMENT OF CANCER

DNA Repair Inhibitors

Approved Indication	Generic Name	Trade Name
certain types of ovarian, fallopian tube, and primary peritoneal cancers	niraparib	Zejula
certain forms of breast and ovarian cancers	olaparib*	Lynparza
certain type of ovarian cancer	rucaparib*	Rubraca
certain type of breast cancer	talazoparib*	Talzenna

Immune Checkpoint Inhibitors

Approved Indication	Generic Name	Trade Name
certain types of bladder, breast, and lung cancers	atezolizumab	Tecentriq
certain types of bladder, kidney, and skin cancers	avelumab	Bavencio
certain type of skin cancer	cemiplimab-rwlc	Libtayo
certain types of bladder cancer and lung cancer	durvalumab	Imfinzi
multiple cancers	ipilimumab	Yervoy
multiple cancers	nivolumab	Opdivo
multiple cancers	pembrolizumab	Keytruda

Bone-remodeling Inhibitors

Approved Indication	Generic Name	Trade Name
potentially lethal complication of advanced cancers*	denosumab	Xgeva

Angiogenesis Inhibitors

Approved Indication	Generic Name	Trade Name
kidney cancer	axitinib	Inlyta
multiple cancers	bevacizumab	Avastin
thyroid cancer; kidney cancer; liver cancer	cabozantinib	Cometriq; Cabometyx
certain type of thyroid cancer; kidney cancer; liver cancer	lenvatinib	Lenvima
kidney cancer; soft tissue sarcomas; gastrointestinal stromal tumors	pazopanib	Votrient
certain types of lung, stomach, and liver cancers	ramucirumab	Cyramza
colorectal cancer; gastrointestinal stromal tumors and liver cancer	regorafenib	Stivarga
kidney cancer; certain type of thyroid cancer	sorafenib	Nexavar
gastrointestinal stromal tumors; kidney cancer; some pancreatic cancers	sunitinib	Sutent
thyroid cancer	vandetanib	Caprelsa
colorectal cancer	ziv-aflibercept	Zaltrap

INCREASING PRECISION

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 types of non-Hodgkin lymphoma	mogamulizumab-kpkc	Poteligeo
certain type of leukemia	moxetumomab pasudotox-tdfk	Lumoxiti
certain form of leukemia; certain form of lymphoma	obinutuzumab	Gazyva
certain leukemias	ofatumumab	Arzerra
certain lymphomas	rituximab	Rituxan
certain type of leukemia	tagraxofusp-erzs	Elzonris

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

* includes companion diagnostic

Some drugs are available in multiple formulations; these have only been listed once.

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

SUPPLEMENTAL TABLE 2 *(continued)*

FDA-APPROVED THERAPEUTICS FOR THE TREATMENT OF CANCER

Cell-signaling Inhibitors

Approved Indication	Generic Name	Trade Name
certain type of breast cancer	abemaciclib	Verzenio
certain 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 breast cancer	alpelisib*	Piqray
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
certain type of lung cancer	dacomitinib*	Vizimpro
some leukemias	dasatinib	Sprycel
certain types of leukemia and non-Hodgkin lymphoma	duvelisib	Copiktra
certain type of bladder cancer	erdafatinib*	Balversa
some lung cancers*; pancreatic cancer	erlotinib	Tarceva
some pancreatic cancers; kidney cancer; noncancerous kidney tumors; HER2+ breast cancers; neuroendocrine tumors	everolimus	Afinitor
lung cancer	gefitinib	Iressa
certain type of leukemia	gilteritinib*	Xospata
certain type of leukemia	glasdegib	Daurismo
certain form of lymphoma and non-Hodgkin lymphoma	ibrutinib	Imbruvica
certain types of leukemia and lymphoma	idelalisib	Zydelig
some leukemias; stomach cancer; certain type of skin cancer	imatinib	Gleevec; Glivec
HER2+ breast cancers	lapatinib	Tykerb
NTRK-positive solid tumors	larotrectinib	Vitrakvi
certain type of lung cancer	lorlatinib*	Lobrena
certain types of leukemia	midostaurin*	Rydapt
certain form of lung cancer	necitumumab	Portrazza
certain type of breast cancer	neratinib	Nerlynx
some leukemias	nilotinib	Tasigna
soft tissue sarcoma	olaratumab	Lartruvo
certain form of lung cancer*	osimertinib	Tagrisso
certain subtype of breast cancer	palbociclib	Ibrance
colon cancer	panitumumab	Vectibix
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

* includes companion diagnostic
Some drugs are available in multiple formulations; these have only been listed once.
Where multiple trade names are used, only the most common have been listed.

SUPPLEMENTAL TABLE 3

SURGICAL AND RADIOTHERAPY TREATMENTS FOR CANCER

TYPE OF SURGICAL PROCEDURE*	DESCRIPTION	APPLICABLE CANCER
Mastectomy	Surgery to remove the entire breast	Breast cancer
Lumpectomy (or partial mastectomy)	Surgery to remove the cancer and some normal tissue around it, but not the breast itself	Breast cancer
Orchiectomy	Surgery to remove one or both testicles	Testicular cancer
Video-Assisted Thoracoscopic Surgery (VATS)	Surgery performed using a small video camera that is introduced into the patient's chest via small incisions	Multiple head, neck, and chest cancers
Laparoscopic surgery	Surgery done with the aid of a laparoscope	Variety of abdominal cancers
Reconstructive surgery	Surgery to restore the function or appearance of organs or tissues that were either removed or changed by cancer treatment	Breast and head and neck cancer
Limb-sparing surgeries	Surgery to remove a tumor in a limb (arm or leg) without removing the whole limb	Sarcoma and other cancers
Partial nephrectomy	Surgery to remove part of one kidney or a kidney tumor, but not an entire kidney	Kidney cancer
The Whipple/modified Whipple procedure	Surgery to remove head of the pancreas, the duodenum, a portion of the stomach, and other nearby tissues	Pancreatic cancer
Total mesorectal excision	Surgery to remove significant length of the bowel around a tumor	Rectal cancer
Nerve-sparing prostatectomy	Surgery to remove part or all of the prostate and some of the tissue around it	Prostate cancer
Transanal Endoscopic Microsurgery (TEM)	Surgery performed through the rectum with specially designed microsurgical instruments to remove rectal tumors and early stage rectal cancers	Rectal cancer
Modified retroperitoneal lymph node dissection	Surgery to remove abdominal lymph nodes	Testicular cancer
Sentinel lymph node biopsies	Surgery to identify, remove, and examine sentinel lymph node to determine whether cancer cells are present	Breast, melanoma, and colorectal cancers
Robotic or computer-assisted surgeries	Surgeries that use robotic systems to aid in procedures	Multiple cancers

TYPE OF SURGICAL 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

SUPPLEMENTAL TABLE 3 *(continued)*

SURGICAL AND RADIOTHERAPY TREATMENTS FOR CANCER

TYPE OF SURGICAL PROCEDURE*	DESCRIPTION	APPLICABLE CANCER
Stereotactic radiosurgery (SRS)	A type of external radiation therapy that uses special equipment to position the patient and advanced computer programs to calculate and deliver precisely a single large dose of radiation to a tumor	Brain metastases
Stereotactic body radiotherapy (SBRT) or Stereotactic ablative radiotherapy (SABR)	Administers very high doses of radiation in a few fractions (usually 5 or less), using several beams of various intensities aimed at different angles to precisely target the tumor anywhere in the body	Liver cancer, lung cancer, pancreatic cancer, spinal metastases, oligometastases, recurrent cancers requiring re-irradiation
Proton therapy	A type of radiation treatment that uses protons to treat cancer	Pediatric cancers, certain unresectable skull base or head and neck cancers, certain CNS tumors, ocular tumors, recurrent cancers requiring re-irradiation, hepatocellular carcinoma, certain retroperitoneal sarcoma **
Particle therapy	A form of external beam radiotherapy using beams of energetic protons, neutrons, or positive ions such as carbon ion for cancer treatment	Carbon ion therapy is being tested for several solid cancers outside of the US
Neoadjuvant or adjuvant radiotherapy	Radiation is delivered either before (neoadjuvant) or after (adjuvant) surgery, sometimes with concurrent systemic therapy	Multiple cancers
Organ preservation approach	Definite radiotherapy +/- chemotherapy that are designed to produce cure while preserving the organ where the tumor is located	Certain head and neck cancers, breast cancer (with lumpectomy), anal cancer, esophageal cancer, bladder cancer

*Delivered alone or in combination with other types of radiation listed in the table with or without concurrent chemotherapy, targeted therapy or hormonal therapy

**ASTRO group 1 guideline

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