AACR CANCER PROGRESS REPORT

2017

Harnessing Research Discoveries to Save Lives

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AACR

American Association for Cancer Research

FINDING CURES TOGETHER®

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A MESSAGE FROM THE AACR

This is an incredibly exciting time for the cancer community. In the United States, overall cancer incidence and death rates are declining, and an increasing number of people are living longer, higher-quality lives after a cancer diagnosis. This progress has been made possible by individuals working across the continuum of cancer research from basic to translational to clinical and population research who are harnessing discoveries to drive advances across the clinical cancer care spectrum and save an increasing number of lives from cancer.

The AACR Cancer Progress Report 2017 provides a comprehensive overview of the progress we are making because of research, much of which is supported by federal investments in the National Institutes of Health (NIH) including the National Cancer Institute (NCI). As highlighted in the report, the pace at which we have harnessed decades of basic research in the field of immunology to develop lifesaving immunotherapeutics in the clinic has been particularly rapid. For example, there has been a surge in the number of types of cancer for which the U.S. Food and Drug Administration (FDA) has approved immunotherapeutics that work by releasing brakes on the natural cancer-killing power of the immune system. In January 2015, they were approved for treating just one type of cancer. As of July 31, 2017, they were approved for treating seven different types of cancer and for treating any type of solid tumor characterized by the presence of a specific molecular signature, or biomarker.

The first ever approval of a therapeutic to treat cancer based solely on its molecular alterations rather than the site of origin was made possible by the remarkable progress in our understanding of cancer biology. As we step further into the era of precision medicine, deepening of our knowledge of the basic molecular underpinnings of cancer will undoubtedly lead to more biomarker-based therapeutics, providing hope for many cancer patients who are awaiting more effective treatment options.

Expanding our wealth of genomic data by analyzing many more patient samples will allow us to make even more advances for patients with cancer around the world. However, the collection, harmonization, and analysis of datasets large enough to achieve these transformational advances will require collaboration and data sharing on an unprecedented scale. Among the new initiatives leading collaborative efforts to generate big data is AACR Project Genomics, Evidence, Neoplasia, Information, Exchange (GENIE). In January 2017, the AACR Project GENIE consortium publicly released nearly 19,000 de-identified genomic records collected from patients who were treated at the eight participating institutions. The goal of this data release is to catalyze new clinical and translational research that will significantly enhance the future utility of precision medicine.

Despite the significant progress made against the many diseases we call cancer, there is a vital need for continued research innovation. This urgency is underscored by the sobering reality that the 5-year relative survival rates for U.S. patients diagnosed with some types of cancer, such as liver cancer, pancreatic cancer, or the aggressive form of brain cancer with which Senator John McCain was recently diagnosed, glioblastoma, have not improved significantly over the past several decades.

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

We now have the scientific knowledge and capability to deliver advances across the continuum of cancer care that were previously unimaginable and will help us save more lives from cancer. Given that in fiscal year (FY) 2016 and FY 2017, the NIH received from Congress its first consecutive, significant funding increases in more than a decade, it is clear that there is also a strong, bipartisan commitment to invest in cancer research and biomedical science on Capitol Hill at a level required to realize the goal of defeating cancer sooner.

Ensuring that biomedical science remains a top priority for our nation's policy makers is vital if we are to continue and accelerate our current pace of progress. Thus, the AACR urges Congress to negotiate a bipartisan budget deal to raise the discretionary budget caps for FY 2018. The shortsighted and restrictive discretionary spending caps that are in place for FY 2018 as a result of the 2011 Budget Control Act will jeopardize the opportunity for the NIH, NCI, and FDA to receive robust, sustained, and predictable annual funding increases in FY 2018 and beyond, and thereby

compromise our nation's ability to make lifesaving progress for patients. In addition, elected leaders must ensure that the funds designated through the 21st Century Cures Act for initiatives such as the Beau Biden Cancer Moonshot are fully appropriated.

The AACR calls on all of its members, and indeed all Americans, to join us in our quest to make cancer research a long-term national priority. Cancer patients, survivors, and their family members, including the eight courageous individuals who have shared their personal experiences in this report, as well as the thousands of others who have been diagnosed with cancer, such as Senator McCain, are depending on us to collaborate in order to develop and expedite the next breakthroughs against cancer.

Michael A. Caligiuri, MD
AACR President

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

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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 37,000 laboratory, translational, and clinical researchers; population scientists; other health care professionals; and patient advocates residing in 108 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 21,900 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.**

EXECUTIVE SUMMARY

Research continues to be our best defense against cancer. It improves survival and quality of life for people around the world by spurring the development of new and better ways to prevent, detect, diagnose, treat, and cure some of the diseases we call cancer.

As the first and largest professional organization in the world dedicated to advancing every aspect of cancer research, from basic science to translational research to clinical research and population science, the American Association for Cancer Research (AACR) is dedicated to increasing public understanding of cancer and the importance of cancer research to public health. It is also committed to advocating for increased federal funding to government agencies that fuel progress against cancer, in particular, the National Institutes of Health (NIH), the National Cancer Institute (NCI), and the U.S. Food and Drug Administration (FDA).

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

CANCER IN 2017

Basic research is the foundation of new and better approaches to cancer prevention, detection, diagnosis, and treatment, which are driving down overall U.S. cancer incidence and death rates and increasing the number of children and adults who are living longer, higher-quality lives after a cancer diagnosis. In fact, the age-adjusted U.S. cancer death rate declined by 25 percent from 1991 to 2014, a reduction that translates into 2.1 million cancer deaths avoided. In addition, the U.S. 5-year relative survival rate for all cancers combined rose from 49 percent in the mid-1970s to 69 percent in 2013, which is the last year for which we have data.

AACR President, 2017–2018

MICHAEL A. CALIGIURI, MD

"Since I was in medical school in the late 1970s, I have seen a transformation in cancer care. This change ... is a result of tremendous advances in basic and applied research."

From 2010 to 2014, overall cancer death rates fell by:

- 1.8% per year for U.S. men
- 1.4% per year for U.S. women
- 1.6% per year for children ages 0 to 14

Even though significant advances have been made, cancer is a growing public health challenge globally. In the United States alone, it is estimated that 1,688,780 new cancer cases will be diagnosed in 2017. This number is projected to rise to 2,255,290 in 2030 largely because cancer is primarily a disease of aging and the segment of the U.S. population age 65 and older is growing. Moreover, the burden of cancer is shouldered disproportionately by certain segments of the population, including racial and ethnic minorities and patients of lower socioeconomic status.

The immense toll of cancer is felt not only through the number of lives it affects each year, but also through its significant economic impact. The direct medical costs of cancer care, which are one measure of the financial impact of cancer, are estimated to have been $87.6 billion in the United States in 2014, the last year for which these data are currently available. With the personal and economic burden of cancer predicted to increase substantially in the next few decades, it is clear that the research that powers progress against cancer is a vital national investment.

PREVENTING CANCER: UNDERSTANDING RISK FACTORS

Decades of research have led to the identification of numerous factors that increase the risk of developing cancer. Exposure to many of these factors can be eliminated or reduced. Thus, it is clear that many cases of cancer could be prevented. In fact, it is estimated that about half of cancer cases worldwide are attributable to preventable causes.

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

The development and implementation of public education and policy initiatives designed to eliminate or reduce exposure to preventable causes of cancer have reduced cancer morbidity and mortality in the United States. For example, such initiatives drove down cigarette smoking rates among U.S. adults from 42 percent in 1965 to 15 percent in 2015. However, some individuals continue to expose themselves to preventable causes of cancer. Thus, we must identify new strategies to enhance the dissemination and implementation of our current knowledge of cancer prevention, in particular among the segments of the population who experience cancer health disparities.

More than 8 million
smoking-related U.S. deaths were prevented from 1964 to 2014 because of declines in cigarette smoking rates.

SCREENING FOR CANCER PREVENTION AND EARLY DETECTION

Research that has deepened our understanding of the biology of cancer initiation and development has led to the development of screening strategies to detect, if present, precancerous lesions or cancer at an early stage of development. Finding precancerous lesions or cancer at an early stage of development makes it more likely that a cancer can be intercepted and 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. Independent groups of experts rigorously evaluate data indicating whether cancer screening tests meet these two criteria before putting forth recommendations about the use of the tests. Not all groups of experts give the same weighting to all the benefits and potential risks, which can result in differences in recommendations from distinct groups. These differences highlight the areas in which more research is needed.

Evidence-based cancer screening recommendations are only one consideration when a person makes decisions about which cancers he or she should be screened for and when. A person's own unique risks for developing each type of cancer, his or her tolerance of the potential risks of a screening test, and his or her general health are also important considerations. Therefore, every individual should consult with health care practitioners to develop a cancer prevention and early detection plan tailored to them.

HARNESSING RESEARCH DISCOVERIES TO SAVE LIVES

The dedicated efforts of individuals working throughout the

biomedical research cycle constantly power the application of discoveries in basic research to advances across the clinical cancer care continuum that are improving survival and quality of life for people around the world.

Among the advances made from August 1, 2016, to July 31, 2017, are the nine new anticancer therapeutics approved for use by the FDA. During this period, the FDA also approved a new optical imaging agent to help visualize cancerous tissue during surgery and new uses for eight previously approved anticancer therapeutics.

Seven of the new anticancer therapeutics approved by the FDA target specific molecules involved in cancer and are referred to as molecularly targeted therapeutics. They are part of the precision medicine revolution in cancer care that is improving the lives of patients like **Evan Freiberg** and **Teri Woodhull** (pp. 66 and 70, respectively).

The other two new therapeutics are immunotherapeutics called checkpoint inhibitors. They work by releasing some of the brakes on the immune system. This group of immunotherapeutics has been shown to yield remarkable and durable responses for some patients with an increasingly diverse array of types of cancer, as highlighted in the report by the experiences of **Carrie Best**, **Bill McCone**, and **Adrienne Skinner** (pp. 86, 82, and 78, respectively).

The research-fueled advances in cancer detection, diagnosis, and treatment are helping more people to survive longer and lead fuller lives after a cancer diagnosis. Despite this progress, cancer survivors often face serious and persistent adverse outcomes, including physical, emotional, and psychosocial challenges as a result of their disease and treatment. Palliation of physical symptoms throughout cancer treatment and through the balance of life, as well as addressing behavioral, emotional, psychological, and social challenges through psycho-oncology, is an important approach to improving the quality of life for cancer patients and survivors.

LOOKING TO THE FUTURE

The significant progress we have made against cancer is rooted in research that has provided us with a deep understanding of cancer biology.

As we look to the future, many researchers today, including **AACR President Michael A. Caligiuri, MD**, (p. 90), feel strongly that we will be able to accelerate the pace of progress by generating, gathering, and analyzing "big data." Harnessing the information contained within data sets that include patient history, diagnostics, genetic tests, treatment decisions, and measured and patient-reported outcomes from large numbers of cancer patients has the potential to provide an even more comprehensive knowledge of the molecular underpinnings of cancer, which will drive the next breakthroughs in cancer prevention, early detection, and treatment.

Big data
can enhance our knowledge of cancer and lead to new breakthroughs.

We will need to ensure that the advances made provide benefit to all. Currently, numerous medically underserved populations, including racial and ethnic minorities and patients of lower socioeconomic status, experience unacceptably higher incidences of some types of cancer than the general population and/or suffer significantly poorer treatment outcomes. As research increases our understanding of the many complex and interrelated causes of cancer health disparities, we will be able to develop and implement new interventions that will save lives, regardless of race, ethnicity, age, gender, socioeconomic status, or place of residence.

WORKING TOGETHER TO OVERCOME CANCER THROUGH PUBLIC POLICY

Federal investments in the NIH, NCI, and FDA have spurred progress against cancer by catalyzing scientific discoveries and facilitating the translation of these discoveries into advances across the continuum of clinical cancer care. However, there are many challenges to overcome if we are to substantially accelerate the pace of progress in cancer prevention, detection, diagnosis, and treatment.

First, we must continue to increase our understanding of the biology of cancer and to develop new approaches to translating this knowledge into health care advances that will increase survival and quality of life for all. To do this, we must ensure that robust, sustained, and predictable federal funding is provided for biomedical research and regulatory science. We must also provide strong support for crosscutting initiatives like the National Cancer Moonshot Initiative, later renamed the Beau Biden Cancer Moonshot. Only by investing in research talent, tools, and infrastructure; supporting regulatory science initiatives; and developing policies that advance patient-centered research and care will we be able to accelerate the pace of progress and realize our goal of preventing and curing all types of cancer.

CALL TO ACTION

During the past two years, Congress has demonstrated a strong, bipartisan commitment to medical research by providing the first consecutive, significant funding increases for the NIH in more than a decade. Because Congress has recognized that medical research is a high national priority, the trajectory of federal funding appropriated for this lifesaving work has now turned a corner and is once again headed in the right direction.

We are at a watershed moment in cancer research, and we cannot allow this positive momentum to be lost. During this time of both unprecedented scientific opportunity and increasing incidence and associated mortality of cancer, Congress must continue to provide robust, sustained, and predictable investments in the NIH. Annual increases in the NIH budget, coupled with a funding increase for the FDA in FY 2018 and beyond, will ensure the acceleration of the pace at which we make research discoveries and translate them into advances that will save more lives from cancer.

However, in order for the NIH, FDA, and other vitally important scientific agencies to receive the resources that are essential to make further strides toward defeating cancer and the many other human diseases that afflict so many Americans, it is going to require that Congress negotiate a bipartisan budget deal to raise the discretionary budget caps for FY 2018. The shortsighted and restrictive discretionary spending caps that are in place for FY 2018 as a result of the 2011 Budget Control Act will compromise our nation's ability to further understand the complexities of cancer and postpone the development of lifesaving therapies for patients.

Continued progress against cancer requires the unwavering support of our elected leaders. Therefore, AACR respectfully urges Congress to:

- **Continue to support robust, sustained, and predictable growth of the NIH budget** by providing an increase of $2 billion for NIH in FY 2018, for a total funding level of $36.2 billion.
- **Increase the FDA budget in FY 2018 to $2.8 billion, an $80 million increase above its FY 2017 level,** to ensure support for regulatory science and to accelerate the pace of development of medical products that are safe and effective.
- **Ensure that funding designated through the 21st Century Cures Act for initiatives and programs, such as the Beau Biden Cancer Moonshot and the FDA Oncology Center of Excellence, is fully appropriated in FY 2018.**
- **Negotiate a bipartisan budget deal to raise the discretionary budget caps for FY 2018 and beyond,** which would allow our nation's policy makers to continue to invest in priority areas, such as the biomedical research funded by the NIH.

Congress can help us transform cancer care, save more lives from cancer, spur economic growth, and maintain the position of the United States as the global leader in science and medical research by providing annual funding increases for the NIH, NCI, and FDA that are robust, sustained, and predictable. Most importantly, this will continue to bring real hope to the millions of people all over the world whose lives are touched by cancer.

A SNAPSHOT OF A YEAR OF PROGRESS

1991

25%

REDUCTION IN U.S. CANCER DEATH RATE

2014

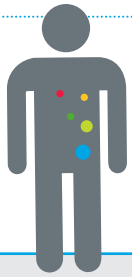
2.1 million lives saved.

Between August 1, 2016, and July 31, 2017, the FDA Approved:

9 **new** anticancer therapeutics.

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

1 **new** optical imaging agent.



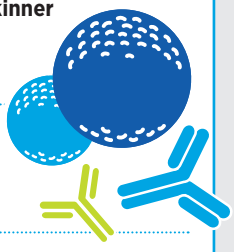
Research Continues to Advance Immunotherapy:

Leading to new and expanded uses for immunotherapeutics. These new treatments are:

allowing patients with Lynch syndrome like **Adrienne Skinner** to live with no evidence of disease, p. 78.

benefiting patients with Merkel cell carcinoma, like **Carrie Best**, p. 86.

effectively treating patients with head and neck cancer, like **Bill McCone**, p. 82.

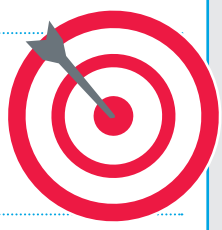


Research Continues to Power Precision Medicine:

Leading to new therapeutics that target specific molecules involved in the cancer process, including:

a PARP inhibitor for treating patients with ovarian cancer, like **Teri Woodhull**, p. 70.

a PDGFR-alpha–targeted therapeutic, which is benefiting patients with soft tissue sarcoma, like **Evan Freiberg**, p. 66.



the first FLT3 inhibitor, which is benefiting patients with acute myeloid leukemia, p. 61.

CANCER IN 2017

In this section you will learn:

- In the United States, the age-adjusted overall cancer death rate is decreasing.
- The reduction in the U.S. cancer death rate from 1991 to 2014 translates into 2.1 million cancer deaths avoided.
- In 2017, 600,920 people are expected to die from cancer in the United States, making it the second most common cause of death.
- Not all segments of the U.S. population have benefited equally from advances against cancer.
- It is projected that the number of new cancer cases diagnosed each year in the United States will almost double by 2030.
- The cost of cancer is enormous, both in the United States and globally.

RESEARCH: DRIVING PROGRESS AGAINST CANCER

Research is the foundation of progress against the many diseases we call cancer. It improves survival and quality of life for people around the world because it is the driving force behind every advance across the clinical cancer care continuum and every legislative action designed to improve public health.

Each advance is the culmination of a complex, multifaceted process that takes many years of hard work by individuals from all segments of the biomedical research community (see sidebar on **The Biomedical Research Community: Driving Progress Together**, p. 9).

Among the advances made across the clinical cancer care continuum from August 1, 2016, to July 31, 2017, are the nine new anticancer therapeutics approved for use by the U.S. Food and Drug Administration (FDA) (see **Table 1**, p. 10). During this period, the FDA also approved a new optical imaging agent to help visualize cancerous tissue during surgery and new uses for eight previously approved anticancer therapeutics.

Advances such as those listed in **Table 1** (see p. 10) are helping drive down U.S. cancer death rates and increase the number of children and adults who survive a cancer diagnosis (2-4) (see **Figure 1**, p. 11). In fact, the age-adjusted U.S. cancer death rate declined by 25 percent from 1991 to 2014, a reduction that translates into 2.1 million cancer deaths avoided (2). In addition, the U.S. 5-year relative survival rate for all cancers combined rose from 49 percent in the mid-1970s to 69 percent in 2013, which is the last year for which we have data (5).

The research that drives progress against cancer is made possible by investments from governments, philanthropic individuals and organizations, and the private sector the world over. In the United States, federal investments in biomedical research and government agencies conducting research, such as the FDA and the Centers for Disease Control and Prevention (CDC), are of particular importance. Most U.S. government investments in biomedical research are administered through the 27 institutes and centers of the National Institutes of Health (NIH). The largest component of the NIH is the National Cancer Institute (NCI), which is the federal government's principal agency for cancer research and training.

CANCER: AN ONGOING CHALLENGE

Although we have made incredible progress against cancer, this collection of diseases continues to be an immense public health challenge worldwide (see sidebar on **Cancer: A Global Challenge**, p. 12). In the United States, it is predicted that 600,920 people will die from some type of cancer in 2017 (2) (see **Table 2**, p. 13). This makes cancer the second most common cause of death in the United States after heart disease.

The Biomedical Research Community: Driving Progress Together

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

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

health care providers;

academic and government researchers from a diverse array of specialties;

biotechnology, pharmaceutical, diagnostics, and medical device companies;

individual citizen advocates and members of advocacy groups;

policy makers;

regulators;

philanthropic organizations and cancer-focused foundations;

federal funding organizations; and

payers.

Adapted from (1)

Table 1

Anticancer Therapeutics Approved by the FDA between August 1, 2016, and July 31, 2017

Angiogenesis Inhibitors

Approved Indication	Generic Name	Trade Name	Formulation
Certain type of liver cancer†	regorafenib	Stivarga	

Cell Signaling Inhibitors

Approved Indication	Generic Name	Trade Name	Formulation
Certain type of lung cancer	brigatinib	Alunbrig	
Certain type of lymphoma†	ibrutinib	Imbruvica	
Certain types of leukemia	midostaurin*	Rydapt	
Soft tissue sarcoma	olaratumab	Lartruvo	
Certain type of breast cancer	ribociclib	Kisqali	
Certain type of lung cancer†	dabrafenib and trametinib*	Tafinlar and Mekinist	
Certain type of breast cancer	neratinib	Nerlynx	

DNA-repair Inhibitors

Approved Indication	Generic Name	Trade Name	Formulation
Certain types of ovarian, fallopian tube, and primary peritoneal cancer	niraparib	Zejula	
Certain type of ovarian cancer	rucaparib*	Rubraca	

Immunotherapeutics

Approved Indication	Generic Name	Trade Name	Formulation
Certain type of lung cancer†	atezolizumab	Tecentriq	
Certain types of bladder cancer† and skin cancer	avelumab	Bavencio	
Certain type of bladder cancer	durvalumab	Imfinzi	
Certain types of head and neck cancer† and bladder cancer†	nivolumab	Opdivo	
Certain types of head and neck cancer†, lymphoma†, bladder cancer†, and solid tumors that are MSI-H‡ or dMMR§	pembrolizumab	Keytruda	

†new use for 2016–2017
* requires a companion diagnostic

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

‡ Microsatellite instability–high
§ Mismatch repair–deficient

Variable Progress between Types of Cancer and Stages of Diagnosis

Among the challenges we face is that the advances we have made have not been uniform for all types and stages of cancer. For example, while the death rates for many of the most commonly diagnosed cancers in the United States—including breast, colorectal, lung, and prostate cancer—have been declining for more than a decade, those for other forms of cancer—most notably brain, liver, and uterine cancer—have been increasing (3). In addition, patients diagnosed when the disease 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 (3).

Given these challenges, 5-year relative survival rates for U.S. patients vary widely depending on both the type of cancer diagnosed and the stage at diagnosis (2, 3) (see **Figure 2**, p. 14).

Disparities in Progress for Distinct Population Groups

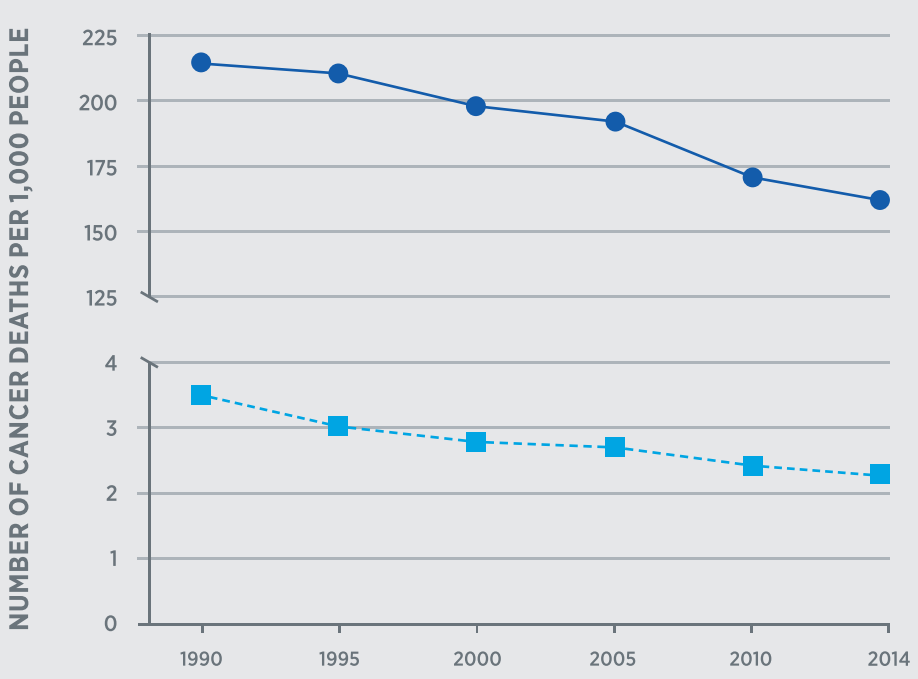
Cancer health disparities are some of the most pressing challenges posed by cancer that we face in the United States today.

According to the NCI, cancer health disparities are adverse differences in cancer measures such as number of new cases, number of existing cases, cancer-related health complications, number of deaths, survivorship and quality of life after cancer treatment, burden of cancer or related health conditions, screening rates, and stage at diagnosis that exist between certain segments of the population (8) (see sidebar on **What Are Cancer Health Disparities?**, p. 15 and the sidebar on **U.S. Cancer Health Disparities**, p. 16).

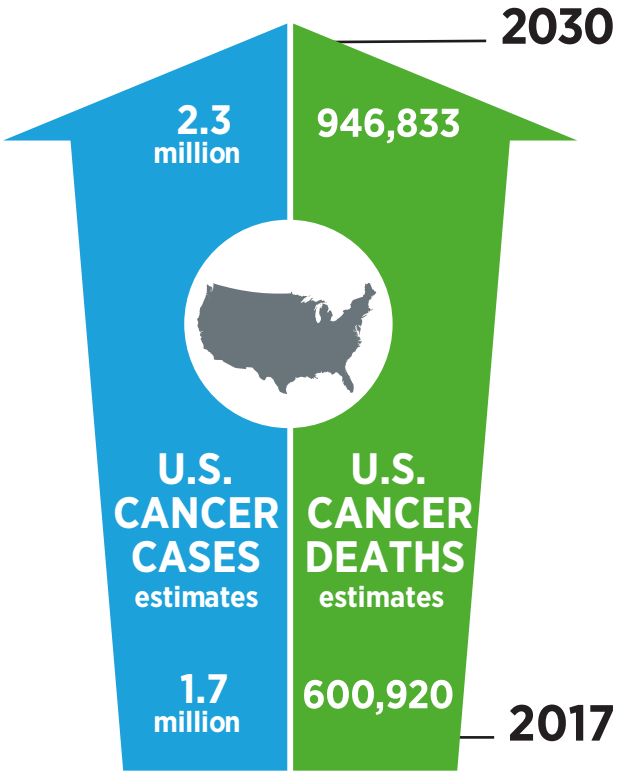
There are many complex and interrelated factors that contribute to U.S. cancer health disparities, which makes it difficult to isolate and study the relative contribution of each (see sidebar on **Why Do Cancer Health Disparities Exist?**, p. 17). However, given that a significant proportion of the U.S. population falls into one or more risk categories, it is important that research into these specific issues continues. One area of intensive research investigation is furthering our understanding of the contribution of biological factors such as genetics to the adverse outcomes for certain U.S. populations. Only with new insights obtained through research and through the inclusion of all segments of the U.S. population in clinical trials will we develop and implement interventions that will eliminate cancer for all.

Figure 1

Making Progress against Cancer



The age-adjusted overall U.S. cancer death rates for both adults (solid blue line) and children (ages 0 to 19) (dashed blue line) have been declining steadily since the early 1990s. In 1990, there were 214.95 cancer deaths per 100,000 U.S. adults. By 2014, the last year for which these data are available, this had dropped to 161.3 per 100,000, a decline of 25 percent. During this same period, the number of childhood deaths from cancer dropped from 3.4 per 100,000 U.S. children to 2.2 per 100,000, a drop of 35 percent (5).



Data from (2, 7)

A Growing Challenge

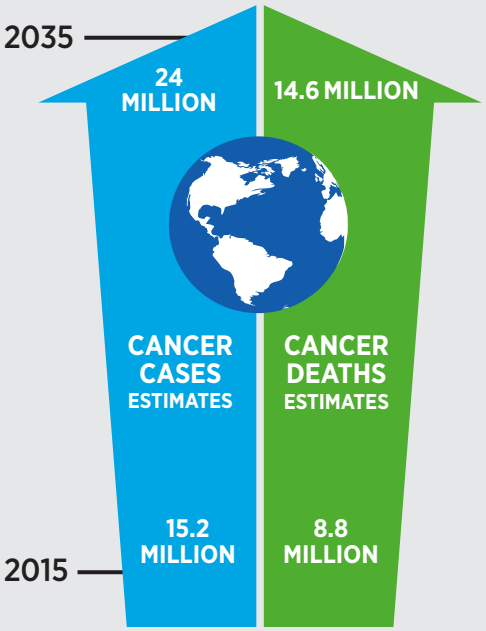
The public health challenge posed by cancer is predicted to grow considerably in the coming decades unless we develop and effectively implement more effective strategies for cancer prevention, early detection, and treatment (7).

In the United States alone, the number of new cancer cases diagnosed each year is expected to almost double by 2030, when it is anticipated that it will reach 2.3 million (2, 7). This is largely because cancer is primarily a disease of aging, 53 percent of U.S. cancer diagnoses occur among those age 65 and older (16), and this segment of the U.S. population is expected to grow from 49.2 million in 2016 to 74.1 million in 2030 (17, 18). Also contributing to the projected increase in the number of U.S. cancer cases are continued use of cigarettes by 15 percent of U.S. adults (19) and high rates of obesity and physical inactivity, which are both linked to some common types of cancer (20).

The United States is not unique in this regard (see sidebar on **Cancer: A Global Challenge**). Thus, it is imperative that the global biomedical research community work together to drive down cancer incidence and mortality.

Cancer: A Global Challenge

The number of global deaths from cancer is rising, as is the proportion of deaths that cancer accounts for (6).



In 2005, cancer accounted for 7.5 million of the 53.6 million deaths worldwide, meaning it accounted for **1 in 7 deaths.**

In 2015, cancer accounted for 8.8 million of the 55.8 million deaths worldwide, meaning it accounted for almost **1 in 6 deaths.**

The devastating impact of cancer will grow significantly in the coming decades if new and more effective approaches to cancer prevention, early detection, and treatment are not developed and effectively implemented (6,7).

Table 2

Estimated Incidence and Mortality for Select Cancers*

	ESTIMATED 2017 INCIDENCE			ESTIMATED 2017 DEATHS		
	Total	Male	Female	Total	Male	Female
All Sites	**1,688,780**	**836,150**	**852,630**	**600,920**	**318,420**	**282,500**
Head and Neck Region						
Brain and other nervous system	23,800	13,450	10,350	16,700	9,620	7,080
Eye and orbit	3,130	1,800	1,330	330	180	150
Tongue	16,400	11,880	4,520	2,400	1,670	730
Mouth	13,210	7,800	5,410	2,580	1,680	900
Pharynx	17,000	13,780	3,220	3,050	2,340	710
Other oral cavity	3,060	2,260	800	1,670	1,310	360
Larynx	13,360	10,570	2,790	3,660	2,940	720
Lung and bronchus	222,500	116,990	105,510	155,870	84,590	71,280
Breast	255,180	2,470	252,710	41,070	460	40,610
Gastrointestinal System						
Esophagus	16,940	13,360	3,580	15,690	12,720	2,970
Stomach	28,000	17,750	10,250	10,960	6,720	4,240
Liver and intrahepatic bile duct	40,710	29,200	11,510	28,920	19,610	9,310
Gallbladder and other biliary	11,740	5,320	6,420	3,830	1,630	2,200
Pancreas	53,670	27,970	25,700	43,090	22,300	20,790
Small intestine	10,190	5,380	4,810	1,390	770	620
Colon and rectum†	95,520	47,700	47,820	50,260	27,150	23,110
Anus, anal canal, and anorectum	8,200	2,950	5,250	1,100	450	650
Urogenital System						
Kidney and renal pelvis	63,990	40,610	23,380	14,400	9,470	4,930
Ovary	22,440		22,440	14,080		14,080
Uterine corpus	61,380		61,380	10,920		10,920
Uterine cervix	12,820		12,820	4,210		4,210
Urinary bladder	79,030	60,490	18,540	16,870	12,240	4,630
Prostate	161,360	161,360		26,730	26,730	
Testis	8,850	8,850		410	410	
Skin						
Skin (excluding basal and squamous)	95,360	57,140	38,220	13,590	9,250	4,340
Melanoma-skin	87,110	52,170	34,940	9,730	6,380	3,350
Hematological System						
Leukemia	62,130	36,290	25,840	24,500	14,300	10,200
Acute lymphocytic leukemia	5,970	3,350	2,620	1,440	800	640
Chronic lymphocytic leukemia	20,110	12,310	7,800	4,660	2,880	1,780
Acute myeloid leukemia	21,380	11,960	9,420	10,590	6,110	4,480
Chronic myeloid leukemia	8,950	5,230	3,720	1,080	610	470
Lymphoma	80,500	44,730	35,770	21,210	12,080	9,130
Hodgkin lymphoma	8,260	4,650	3,610	1,070	630	440
Non-Hodgkin lymphoma	72,240	40,080	32,160	20,140	11,450	8,690
Myeloma	30,280	17,490	12,790	12,590	6,660	5,930
Other Cancers						
Bones and joints	3,260	1,820	1,440	1,550	890	660
Soft tissue (including heart)	12,390	6,890	5,500	4,990	2,670	2,320

*Rounded to the nearest 10; estimated new cases exclude basal cell and squamous cell skin cancers and in situ carcinomas except urinary bladder. About 63,410 cases of carcinoma in situ of the female breast and 74,680 cases of melanoma in situ will be newly diagnosed in 2017. †Estimated deaths for colon and rectal cancers are combined. ‡More deaths than cases may reflect lack of specificity in recording underlying cause of death on death certificates and/or an undercount in the case estimate.

Source: Estimated new cases are based on cancer incidence rates from 49 states and the District of Columbia during 1995-2013 as reported by the North American Association of Central Cancer Registries (NAACCR), representing about 98% of the U.S. population. Estimated deaths are based on U.S. mortality data during 1997-2013, National Center for Health Statistics, Centers for Disease Control and Prevention.

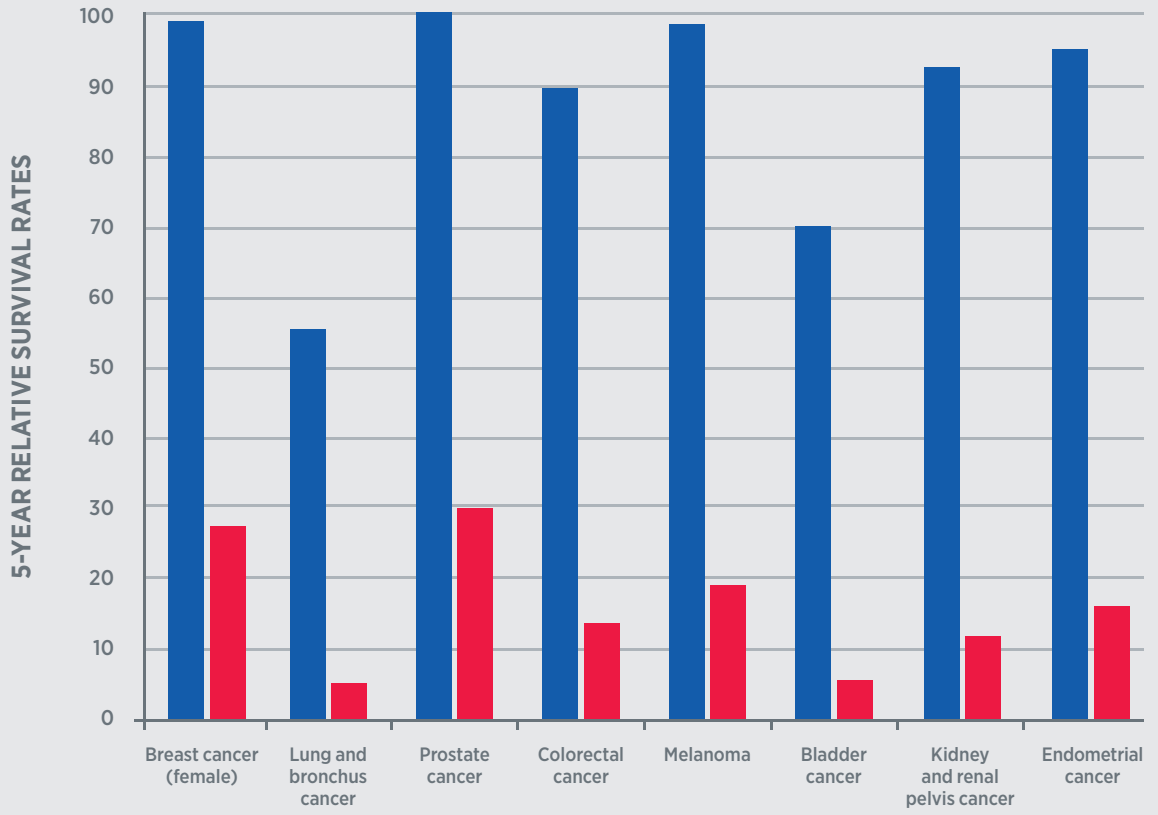
CANCER: A COSTLY DISEASE. RESEARCH: A VITAL INVESTMENT

Cancer exerts an immense toll, both as a result of the number of lives it affects each year and through its significant economic impact. The direct medical costs of cancer care are one measure of the financial impact of cancer, and in the United States alone, they are estimated to have been $87.6 billion in 2014, the last year for which these data are currently available (2). Although this number does not include the indirect costs of lost productivity due to cancer-related morbidity and mortality, it stands in stark contrast to the budget that the NIH received that same year, which was $30.1 billion, of which $4.9 billion went to the NCI.

With the number of cancer cases predicted to increase substantially in the next few decades, it is anticipated

Figure 2

Cancer Poses Varying Challenges



Even though we have made significant progress against cancer, the progress has not been uniform for all types and stages of cancer. For example, as shown here, the 5-year relative survival rates for patients in the United States diagnosed with the eight most common types of solid tumor vary depending on the type of cancer diagnosed. They also vary depending on the stage of disease at diagnosis; in all cases, 5-year relative survival is substantially lower for those diagnosed when the disease has spread, or metastasized, to distant sites (red bars) than it is for those diagnosed when the disease remains confined entirely to the organ of origin (blue bars).

Data from (5)

What Are Cancer Health Disparities?

According to the National Cancer Institute, cancer health disparities in the United States are adverse differences in cancer measures such as incidence (number of new cases), prevalence (number of existing cases), morbidity (cancer-related health complications), mortality (number of deaths), survivorship and quality of life after cancer treatment, burden of cancer or related health conditions, screening rates, and stage at diagnosis that exist between certain segments of the population (8), including:

racial and ethnic minority groups;

individuals of different ancestry;

individuals of low socioeconomic status;

individuals who lack or have limited health insurance coverage;

residents in certain geographic locations, including rural areas;

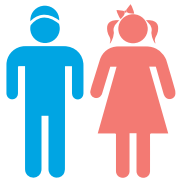
immigrants;

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

refugees or asylum seekers;

individuals with disabilities;

adolescents and young adults; and



the elderly.

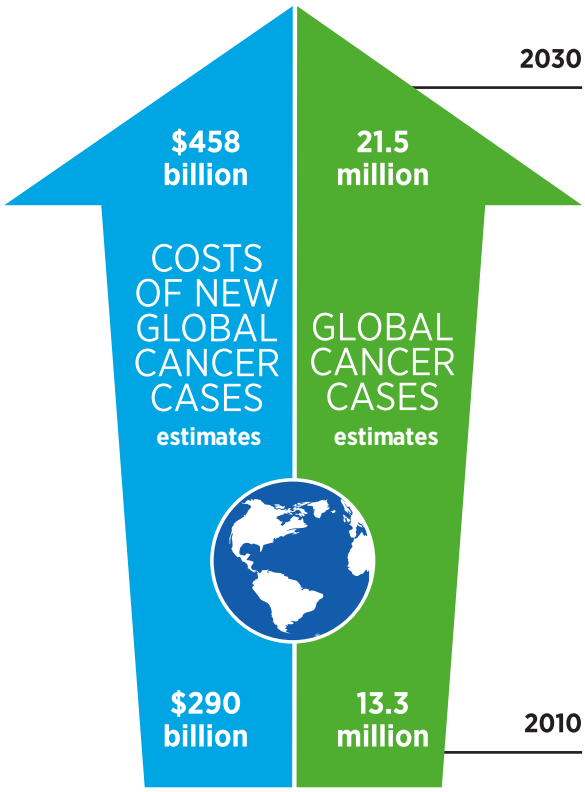
Adapted from (1)

U.S. Cancer Health Disparities

Great strides have been made in cancer prevention, detection, diagnosis, treatment, and, in some cases, cures. However, not everyone has benefited equally from the advances and adverse differences in numerous cancer measures exist among certain segments of the U.S. population (see sidebar on What Are Cancer Health Disparities? p. 15). Some recently identified examples of cancer health disparities are highlighted here:

MORE THAN **DOUBLE**	Black men have a prostate cancer death rate that is more than double that for men of any other racial or ethnic group (3).
24% MORE LIKELY	Hispanic children are 24 percent more likely to develop leukemia than non-Hispanic children (9).
7X	In Union County, Florida, the overall cancer death rate is seven times higher than it is in Summit County, Colorado (10).
50% LESS LIKELY	Early-stage ovarian cancer patients of low socioeconomic status are 50 percent less likely to receive recommended care than those of high socioeconomic status (11).
MORE THAN **40%** MORE LIKELY	Patients with cancer who have Medicaid coverage or no insurance are more than 40 percent more likely to die from their disease than those who have non-Medicaid insurance (12).
3X	Women living with a same-sex relationship partner are three times more likely to die from breast cancer than women living with a male spouse or cohabiting relationship partner (13).
22% LOWER	Adolescents and young adults (ages 15 to 39) with acute myeloid leukemia have a 5-year relative survival rate that is 22 percent lower than that for children (ages 1 to 14) (14).
29% LESS LIKELY	Adults who have an intellectual disability are 29 percent less likely to be up to date with colorectal cancer screening recommendations than those without this disability (15).

that the economic burden will rise sharply too (21). This 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. While the consecutive $2 billion increases for the NIH budget in fiscal year (FY) 2016 and FY 2017 were a welcome boost, to maintain a vibrant cancer research enterprise it is imperative that Congress 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, and FDA, in the years ahead.

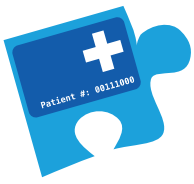


Data from (21)

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; and

exposure to environmental cancer risk factors;

clinical trial participation;

health literacy.

COMPREHENDING CANCER DEVELOPMENT

In this section you will learn:

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

Discoveries across the breadth of biomedical research, from population science and basic research to translational and clinical research, have led to our current comprehension of how cancer arises and develops (see sidebar on **What Is Basic Research and How Does It Drive Progress against Cancer?**, p. 19).

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

CANCER DEVELOPMENT: INFLUENCES INSIDE THE CELL

The normal behavior of each cell in the human body is controlled by the genetic material within it. The genetic material comprises chains of deoxyribonucleic (DNA) units arranged in a particular order and packaged into condensed structures called chromosomes, inside the cell's nucleus (see sidebar on **Genetic and Epigenetic Control of Cell Function**, p. 20). The order of the DNA units as well as its three-dimensional structure dictates which protein and how much of it is made by each cell.

Alterations in the DNA sequence, referred to as mutations, can disrupt normal protein function; they are the leading cause of cancer development (see sidebar on **Genetic Mutations**, p. 21). Cancer-associated mutations most commonly affect three types of genes: oncogenes, tumor suppressors, and DNA repair genes. Mutations in oncogenes promote cell multiplication while mutations in tumor suppressor and DNA repair genes directly or indirectly release the normal brakes that keep cell multiplication in check in healthy cells. Each person's cancer has a unique combination of mutations, and as a cancer progresses, additional mutations accumulate. The number of cells within a growing tumor that carry a given mutation depends on when the mutation was acquired during tumor growth. Thus, even within the same tumor, different cancer cells often have different genetic mutations. This variation, or heterogeneity, within a tumor or between a primary and metastatic tumor is a leading cause of resistance to treatment and thereby disease progression.

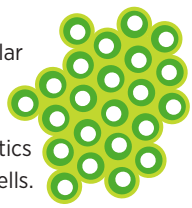
Although 5 to 10 percent of cancer-causing mutations can be inherited (see **Table 3**, p. 22), most are acquired over an individual's lifetime due to errors arising during normal cell multiplication or as a result of environmental

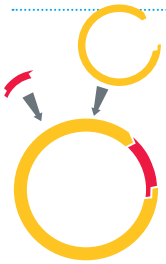
What is Basic Research and How Does it Drive Progress against Cancer?

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, and has been fundamental to our understanding and treatment of human diseases including cancer. The NIH spends more than half of its budget supporting basic research (22). Selected examples of basic research discoveries that have transformed the field of cancer research are:

Discovery of DNA and its building blocks (bases) in the 1800s, followed by the groundbreaking discovery of its 3-dimensional structure in 1953, paved the way for understanding genetic mutations, the underlying basis of most cancers.

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





Recombinant DNA technology, a concept that drives modern biotechnology, is based entirely upon basic research in bacterial biochemistry.

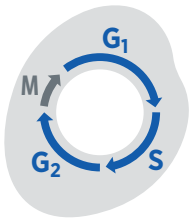
Development of CRISPR-associated protein-9 nuclease has revolutionized the field of gene editing, and its utility to treat genetic diseases, including cancer, is being investigated.

Sources of Genetic Mutations

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

Five to 10 percent of all new U.S. cancer cases are linked to genetic mutations present in each cell of the body from birth (23, 24).

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 as a result of exposure to factors that damage genetic material, such as toxicants in tobacco smoke and ultraviolet (UV) light from the sun (see **Figure 4**, p. 26).

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

Adapted from (25)

exposures or lifestyle factors (see sidebar on **Sources of Genetic Mutations**, p. 19).

Not all mutations acquired by a cell lead to cancer. In fact, the identity, 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 sites for medical intervention to prevent cancer, detect it early, or treat progressive disease. In general, the further a cancer has progressed, the harder it is to stop the chain of events that leads to the emergence of metastatic disease, which is the cause of most deaths from solid tumors.

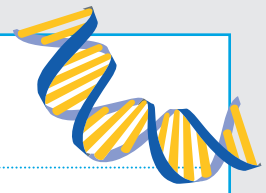
In addition to genetic mutations, changes in the physical structure of DNA caused by modification of the DNA and the proteins associated with it, termed epigenetic modifications, are frequently detected in cancer cells (see sidebar on **Genetic and Epigenetic Control of Cell Function**). Epigenetic modifications regulate how and when our genes are turned "on" or "off" and can be made by specialized proteins that "add" or "erase" unique chemical modifications on DNA and/or histones (26). In contrast to genetic mutations, epigenetic changes are often reversible, providing an attractive opportunity for therapeutic intervention. Our understanding of the role of epigenetics in cancer is, however, still incomplete, and continued research is needed to reveal the real therapeutic potential of the cancer epigenome.

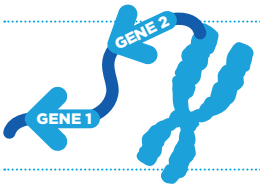
CANCER DEVELOPMENT: INFLUENCES OUTSIDE THE CELL

Cancer is primarily caused by the disruption of normal cellular functions through genetic and epigenetic changes.

Genetic and Epigenetic Control of Cell Function

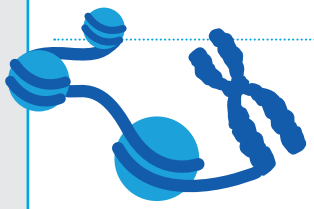
The genetic material of a cell comprises strings of four **deoxyribonucleic acid (DNA)** units called bases.





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 chemical marks, called **epigenetic marks**, on the DNA and histones together determine whether a gene is accessible for reading. The sum of these chemical marks across the entire genome is called the **epigenome**.

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

Adapted from (1)

Once a tumor is initiated, however, complex interactions between cancer cells and their surrounding environment—known as the tumor microenvironment—can contribute to disease progression.

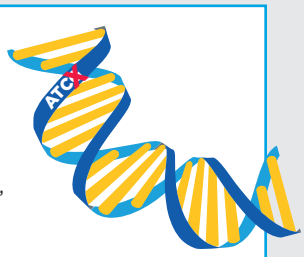
The tumor microenvironment is a specialized niche surrounding the cancer cells (see sidebar on **Cancer Growth: Local and Global Influences**, p. 23). Bidirectional communication between cancer cells and the tumor microenvironment affect cell multiplication, tumor heterogeneity, and tumor metastasis (27, 28). Furthermore, the tumor microenvironment can shelter cancer cells from the effects of radiation, chemotherapy, and immunotherapy thereby rendering them resistant to treatment (29). Future studies are likely to identify additional cellular and molecular mechanisms by which the tumor microenvironment interacts with cancer cells and may help us develop new and improved therapeutics.

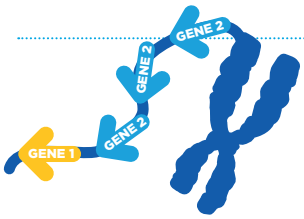
Genetic Mutations

Below are some of the types of genetic mutation known to lead to cancer. Of note, genetic mutations do not always result in cancer.

Single base changes

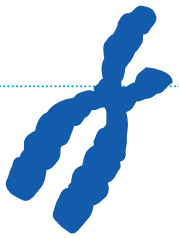
- Some mutations can lead to the generation of altered versions of normal proteins, and these may cause cancer to develop.
- Deletion or insertion of a single base can result in new proteins or loss of protein function, which can lead to cancer.





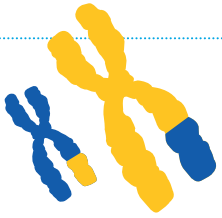
Extra copies of genes (gene amplification)

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



Large deletions

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



Genetic recombination

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

Mutations that alter the epigenome

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

Adapted from (1)

Table 3

Inherited Cancer Risk

Cancers	Syndrome	Associated Gene(s)
Leukemias and lymphomas	Ataxia telangiectasia	*ATM*
Basal cell carcinoma and medulloblastoma	Basal cell nevus syndrome	*PTCH1, PTCH2, SUFU*
All cancers	Bloom syndrome	*BLM*
Breast, ovarian, pancreatic, and prostate cancers	Breast-ovarian cancer syndrome	*BRCA1, BRCA2*
Breast, thyroid, and endometrial cancers	Cowden syndrome	*PTEN*
Breast and stomach cancers	Diffuse gastric and lobular breast cancer syndrome	*CDH1*
Colorectal cancer, medulloblastoma	Familial adenomatous polyposis	*APC*
Melanoma and pancreatic cancer	Familial atypical multiple mole–melanoma syndrome	*CDKN2A*
Glioblastoma and melanoma	Familial glioma-melanoma syndrome	*CDKN2A*
Retinal cancer, pineoblastoma, and bone and soft tissue sarcomas	Retinoblastoma predisposition syndrome	*RB1*
Leukemia and myelodysplastic syndrome (MDS)	Inherited bone marrow failure syndromes, such as Fanconi's anemia and telomere syndromes	*FANCC, FANC, FANCB, FANCS, BRCA1, TERT, TERC*
Kidney cancer and uterine fibroids	Hereditary leiomyomatosis and renal cell cancer	*FH*
Pancreatic cancer	Hereditary pancreatitis/familial pancreatitis	*PRSS1, SPINK1*
Leukemias, breast cancer, glioblastoma, choroid plexus carcinoma, adrenocortical carcinoma, and bone and soft tissue cancers	Li-Fraumeni syndrome	*TP53*
Low grade gliomas, neurofibromas, neurofibrosarcomas, meningiomas, and ependymomas	Neurofibromatosis type I and neurofibromatosis type II	*NF1 and NF2*
Glioblastoma, colorectal cancer, and endometrial cancer	Brain tumor polyposis type I	*MLH1, PMS2*
Medulloblastoma, abdominal desmoid tumors, and colorectal cancer	Brain tumor polyposis type II	*APC*
Colorectal and endometrial cancers	Lynch syndrome	*EPCAM, MLH1, MSH2, MSH6, PMS2*
Rhabdoid tumors of brain, kidney, and extra-renal sites	Rhabdoid predisposition syndrome	*hSNFS, INI1*
Subependymal giant cell astrocytoma, renal angiolipomas, and cardiac rhabdomyomas	Tuberous sclerosis complex	*TSC1 and TSC2*
Leukemias, lymphomas, and MDS	Hereditary myeloid malignancy syndromes, such as familial MDS/acute myeloid leukemias	*RUNX1, GATA2, CEBPA, ETV6, DDX41, ANKRD26, ATG2B/GSKIP*
Pineoblastoma, pleuro-pulmonary blastoma, lymphoma and glioblastoma	DICER syndrome	*DICER1*
Pancreatic cancers, pituitary adenomas, 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

CANCER DEVELOPMENT: INTEGRATING OUR KNOWLEDGE

Knowledge is our greatest strength in driving progress against cancer. Knowing "why" a cancer develops, will help us determine "how" to treat it. For example, comprehensive analyses of human cancer genomes over the past decade revealed several genetic changes associated with a variety of cancers. These discoveries led to the development of a series of therapeutics targeted to rectifying the cellular changes that arise due to the mutations.

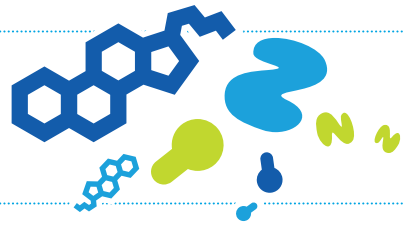
Cancer Growth: Local and Global Influences

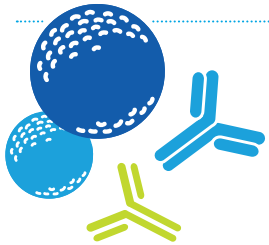
Solid tumors are much more complex than an isolated mass of proliferating cancer cells because cancer initiation, development, and progression are strongly influenced by interactions among cancer cells and numerous factors in their environment. Among the components of the tumor microenvironment are normal parts of the tissue in which the cancer is growing, systemic factors that transiently percolate through the tissue, and cells that are actively recruited to the tissue.

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

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

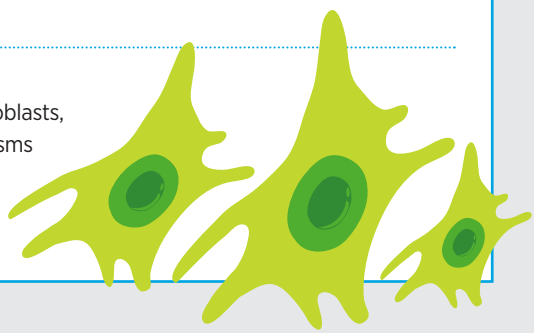
Systemic factors in the circulation, such as hormones and nutrients, influence the development and growth of cancer.





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

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



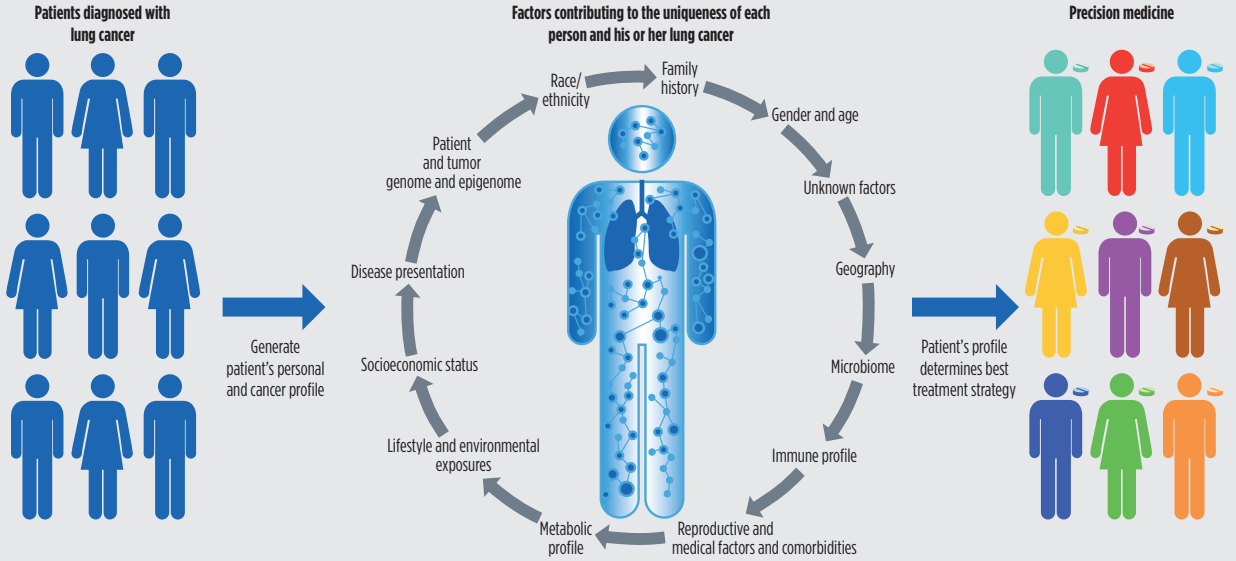
Adapted from (30)

We have also learned that each person's cancer is unique, in part because it is influenced by a patient's biological characteristics and lifestyle factors. As a result, we have seen a major shift in treatment from a "one size fits all" to a more personalized approach. Precision medicine aims to tailor each person's health care to the prevention and/or treatment strategies most likely to be of benefit, sparing each person the cost of and potential harms from prevention interventions and/or treatments that are unlikely to benefit him or her (see **Figure 3**).

Over the past decade, we have made significant progress in how we understand and treat the complex group of diseases we call cancer. Nevertheless, our current knowledge of cancer-causing genetic, lifestyle, and environmental risks is incomplete and ongoing research will continue to uncover additional cellular and molecular alterations that lead to cancer development. An area of primary focus is understanding the biological basis for disparities in cancer incidence and outcomes among certain segments of the U.S. population (see sidebar on **U.S. Cancer Health Disparities**, p. 16). Concerted efforts are needed from all sectors of the biomedical research community to ensure that scientific discoveries benefit the entire population.

Figure 3

Precision Medicine



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

PREVENTING CANCER: UNDERSTANDING RISK FACTORS

In this section you will learn:

- More than half of global cancer cases are a result of preventable causes.
- Not using tobacco is the single best way a person can prevent cancer from developing.
- About 20 percent of U.S. cancer diagnoses are related to people being overweight or obese, being physically inactive, and/or consuming a poor diet.
- Many cases of skin cancer could be prevented by protecting the skin from ultraviolet radiation from the sun and indoor tanning devices.
- The number of U.S. cancer cases attributable to human papillomavirus (HPV) infection is rising, but most U.S. adolescents have not received the full HPV vaccine course.
- There are disparities in the burden of cancer attributable to preventable causes among certain segments of the U.S. population.

Factors that increase the chance of developing cancer are referred to as cancer risk factors. These factors can alter the genetic or epigenetic information in our cells, which may directly lead to cancer development or increase an individual's chance of developing cancer later in life. Many of the factors that increase a person's risk of developing cancer, such as smoking, are also associated with worse outcomes after a cancer diagnosis (see **Modifying Behaviors to Improve Outcomes**, p. 88).

Decades of basic, epidemiologic, and clinical research have led to the identification of numerous cancer risk factors (see **Figure 4**, p. 26). As a result of this work, we know that more than half of all global cancer cases are attributable to preventable causes, including tobacco use, poor diet, physical inactivity, and obesity (20, 31). In addition, vaccination against infection with the human papillomavirus (HPV) and decreasing exposure to ultraviolet (UV) radiation from the sun and indoor tanning devices can further reduce the burden of certain types of cancer (31). Ongoing research may uncover additional cancer risk factors; one area of intensive research investigation is understanding how early life experiences may contribute to cancer development in adulthood (32).

Many cancer risk factors are also risk factors for other chronic diseases, such as cardiovascular disease, respiratory diseases, and diabetes. Therefore, reducing or eliminating exposure to these factors through behavior modification or public education and policy initiative implementation has the potential to reduce the burden of both cancer and other diseases.

In the United States, many of the greatest reductions in cancer morbidity and mortality have been achieved through the implementation of effective public education and policy initiatives. For example, such initiatives drove down cigarette smoking rates among U.S. adults by greater that twofold from 1965 to 2015 (34). However, even today, every three out of 10 cancer deaths are caused by cigarette smoking, and lung cancer is still the leading cause of cancer-related deaths for both men and women (35). Thus, it is imperative that we identify strategies to enhance the dissemination and implementation of our current knowledge of cancer prevention. We also need to develop, disseminate, and implement more effective evidence-based practices that reduce risky behaviors in all population groups.

ELIMINATE TOBACCO USE

Tobacco use is the leading preventable cause of cancer and cancer-related deaths. This is because use of tobacco, or exposure to secondhand smoke, exposes people to many harmful chemicals, including more than 60 different chemicals called carcinogens that can cause cancer by damaging DNA, increasing the chances that it will acquire a mutation (35).

Smoking is linked to 17 different types of cancers in addition to lung cancers, and in 2017, it is estimated that it will cause about 190,500 cancer deaths (see **Figure 5**, p. 27) (37, 38). Even individuals who smoke fewer than one cigarette per day over their lifetime have higher risk of death than nonsmokers and cessation at any age can reduce the risk of cancer occurrence and cancer-related death (34, 39). Therefore, one of the most effective ways a person can lower his or her risk of developing cancer, as well as other smoking-related conditions such as cardiovascular, metabolic, and lung diseases, is to avoid or eliminate tobacco use.

More than 7 million

people every year die as a result of tobacco use (36).

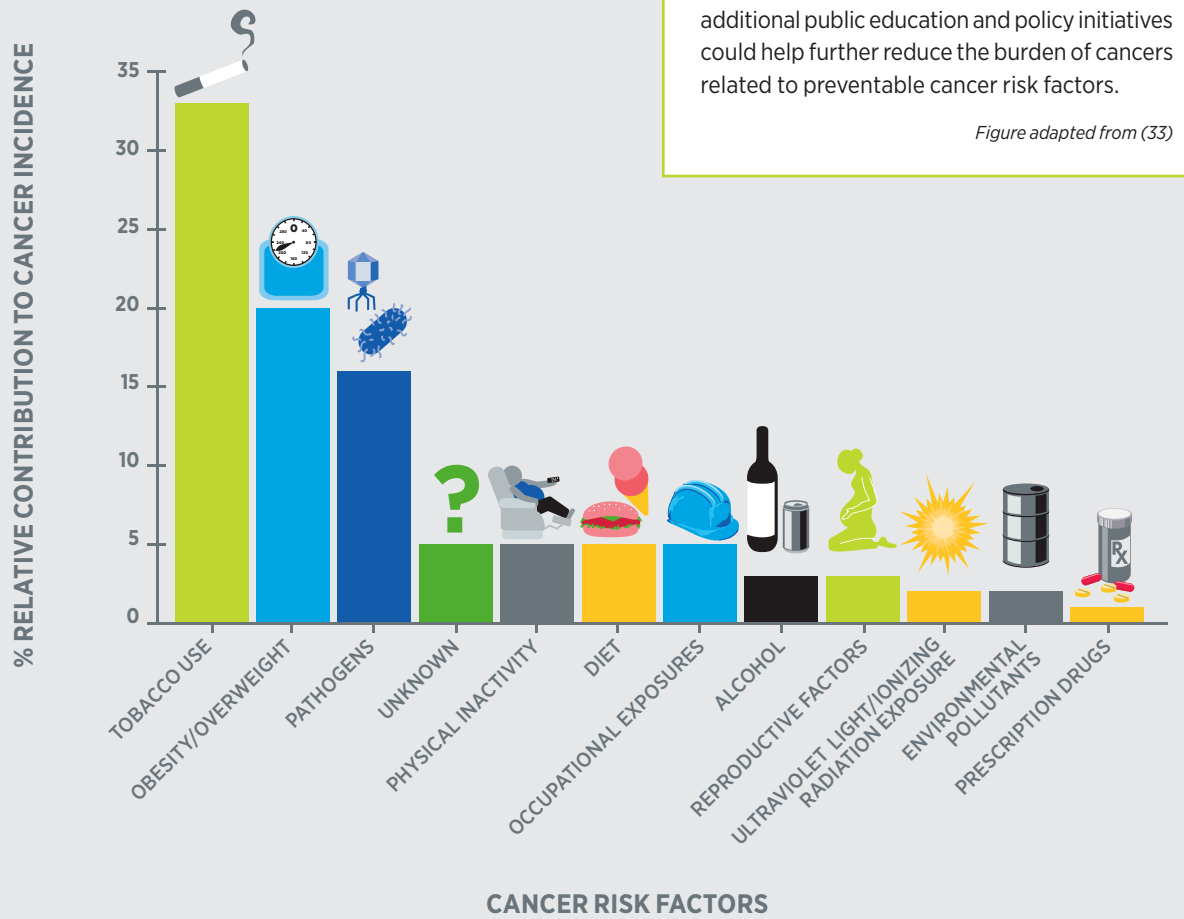
Since the relationship between tobacco use and cancer was first brought to the public's attention in 1964, development and implementation of major public education and policy initiatives have significantly lowered cigarette smoking rates among U.S. adults. In fact, it is estimated that from 2000 to 2015, total cigarette consumption decreased by over 38 percent (41). During the same period, use of several tobacco products among high school students also declined sharply: In 1999, more than 40 percent of high school students reported being current users of cigarettes, cigars, or smokeless tobacco compared with just 18 percent in 2015 (42).

Figure 4

Risky Business

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.

Figure adapted from (33)



We have made major strides in reducing the public health burden due to smoking. Researchers estimate that more than 8 million smoking-related deaths were prevented in the United States from 1964 to 2014 because of declines in cigarette smoking rates (44). However, disparities in cigarette smoking rates and smoking-related health outcomes persist among certain segments of the U.S. population. For example, cigarette smoking rates are much higher among individuals with serious mental health and substance-abuse issues (19, 31). In addition, smoking-related cancer deaths vary across states, with the highest rates being in southern states, where up to 40 percent of cancer deaths in men are caused by smoking (45). These estimates are vital for developing and implementing effective tobacco control and cessation programs.

The use of tobacco products other than cigarettes can also cause cancer. Use of such products, which include cigars,

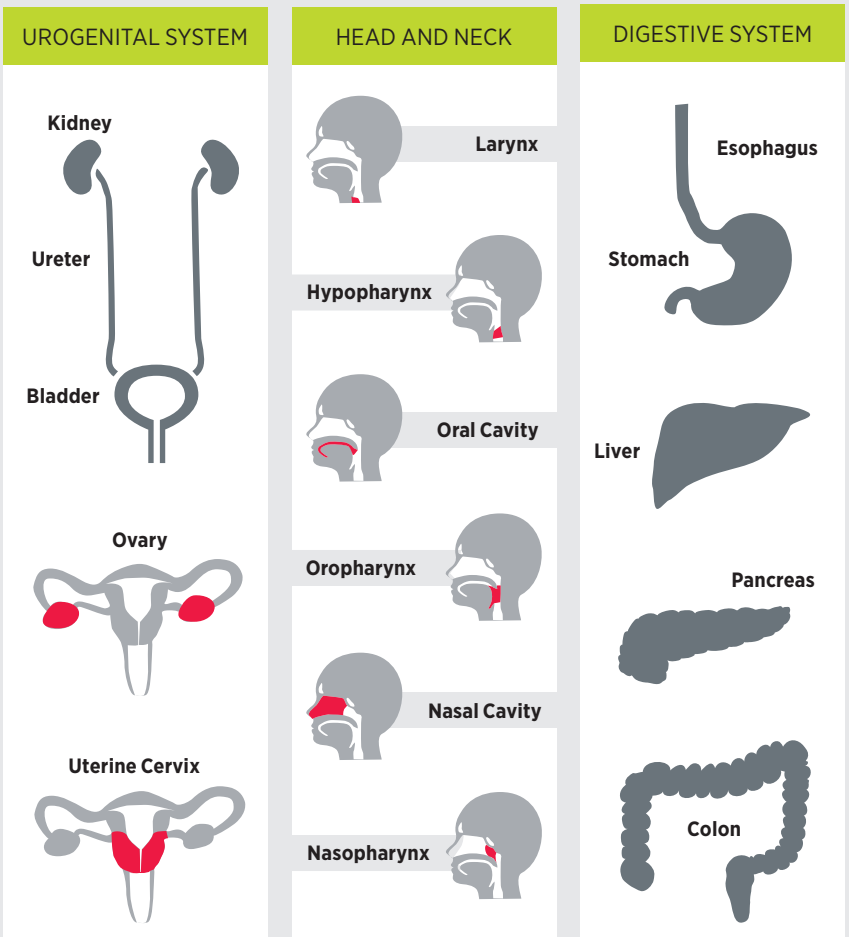
FDA APPROVED

350,000

U.S. youths, were prevented from smoking during 2014–2016 through the FDA's "The Real Cost" campaign (43).

Figure 5

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)

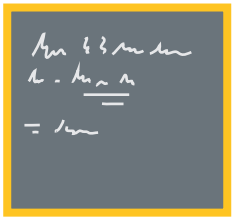
Tobacco-related cancer incidence and death rates are highest in counties with the highest level of **poverty** (46).

smokeless tobacco products (e.g., chewing tobacco and snuff), and pipe tobacco, increased from 2000 to 2015 (38). Electronic cigarettes (e-cigarettes) are a rapidly emerging tobacco product that expose users to a number of harmful chemicals that are known to have adverse health effects. Given that currently we have limited understanding of the long-term effects of e-cigarette use, the U.S. Surgeon General has expressed major concerns about the rise in

E-Cigarettes: A Report from the U.S. Surgeon General

Electronic cigarettes (e-cigarettes) are a rapidly emerging form of electronic nicotine delivery system (ENDS) that deliver nicotine, flavorings, and other additives to users via an inhaled aerosol. The increase in e-cigarette use among youth and young adults has become a public health concern and prompted the U.S. Surgeon General to issue a report that offers a list of goals intended to minimize the public health threat posed by these products (47).

Goal 1. First, Do No Harm | Include e-cigarettes in policies and programs related to conventional cigarette smoking while educating the public about the health risks using evidence-based messages.



Goal 2. Provide Information about the Dangers of E-Cigarette Use among Youth and Young Adults | Educate parents, teachers, and coaches as well as health professionals about the risks of e-cigarette use among youth and young adults.

Goal 3. Continue to Regulate E-Cigarettes at the Federal Level to Protect Public Health | Implement FDA regulatory authority over the manufacturing, marketing, and distribution of e-cigarettes.

Goal 4. Promote Programs and Policies at the State and Local Levels to Prevent E-Cigarette Use among Youth and Young Adults | Identify best strategies to implement population-level regulations to reduce e-cigarette use among youth and young adults; include e-cigarettes in smoke-free indoor air policies; restrict youth access to retailers; establish packaging requirements.

Goal 5. Curb Advertising and Marketing That Encourage Youth and Young Adults to Use E-Cigarettes | Restrict advertising and marketing that cater to the younger generation.

Goal 6. Expand Surveillance, Research, and Evaluation Related to E-Cigarettes | Enhance e-cigarette surveillance, research, and evaluation.

popularity of e-cigarettes among youth and young adults (47) (see sidebar on **E-cigarettes: A Report from the U.S. Surgeon General**, p. 28). Encouragingly, although e-cigarette use rose sharply among high school students from 1.5 percent in 2011 to 16 percent in 2015 (48), the most recent data show a decline in usage to 11.3 percent in 2016 (49).

Since tobacco use and addiction mostly begin during youth and young adulthood, more research into the health consequences of using e-cigarettes and water pipes is urgently needed (50). In particular, we need to fully understand whether e-cigarettes have value as cigarette-

In July 2017, New Jersey became the third U.S. state to pass legislation raising the minimum age of legal access to tobacco products to 21; if this were done nationwide, it is estimated that there would be

45,000 fewer

lung cancer deaths among people born between 2000 and 2019 (40).

Enhancing Tobacco Control through FDA Regulation

The U.S. Food and Drug Administration (FDA) has had the authority to regulate tobacco products since passage of the 2009 Family Smoking Prevention and Tobacco Control Act. While the agency exercised regulatory authority over some of these products, such as cigarettes, others remained unregulated—until now. In 2016, the FDA extended its authority to cover all tobacco-based products. However, legal challenges raised by the vaping and tobacco industry have put some aspects of this deeming rule in jeopardy. The rule:

Permits FDA regulation of vaporizers, vape pens, cigars, hookah pens, hookah pipes, e-cigarettes, e-pipes, and all other electronic nicotine delivery systems, as well as future tobacco products not yet on the market.

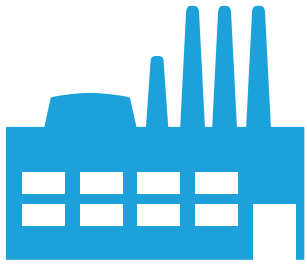
Requires a premarket review process and authorization of new tobacco products that reviews manufacturers' claims and requires the disclosure of ingredients and reporting of harmful or potentially harmful components.

Prohibits the sale of tobacco products to individuals under the age of 18 and requires the display of health warnings in advertisements and on tobacco and tobacco-related products.

Prohibits the distribution of free samples.

Defines content and size of warning labels and requires additional warnings for cigar packaging.

Defines establishments that mix or prepare e-liquids or create or modify aerosolizing apparatus for direct sale to consumers as tobacco product manufacturers that are subject to regulation as manufacturers.



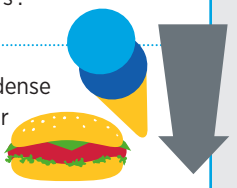
Adapted from (30)

Reduce Your Risk for Cancers Linked to Being Overweight or Obese, Being Inactive, and/or Consuming a Poor Diet

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

Be as lean as possible without becoming underweight, because 14 types of cancer have been causally linked to being obese or overweight (see **Figure 6**, p. 31).

Be physically active for at least 30 minutes every day, because regular physical activity can decrease risk for certain cancers .



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

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

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

If consumed at all, limit alcoholic drinks, because alcohol consumption can increase risk for six types of cancer: breast, colorectal, esophageal, liver, stomach, and mouth/throat cancers.

Source: www.wcrf.org/int/research-we-fund/our-cancer-prevention-recommendations
Adapted from (25)

smoking cessation aids and how they affect use of other tobacco products by smokers and nonsmokers (51).

Even though smoking rates among U.S. adults and youths have declined, it is clear that researchers, clinicians, advocates, and policy makers must continue to work together if we are to eradicate one of the biggest threats to public health. One step to achieving this goal is the decision by the FDA to extend its regulatory oversight to all tobacco products, including e-cigarettes, cigars, pipe tobacco, and hookah tobacco (see sidebar on **Enhancing Tobacco Control through FDA Regulation**, p. 29). Additional strategies, such as further raising taxes on prices and/or adding prominent pictorial warning labels on cigarette packs, also need to be evaluated (38, 52). Moreover, we need to use current tobacco cessation strategies more widely because approaches such as use of nicotine replacement therapy and prescription medication as well as counseling have been shown to be effective in enhancing the chances of long-term abstinence from smoking (38).

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

Researchers estimate that 20 percent of all cancers diagnosed in the United States, including some of the most deadly types of cancer such as pancreatic cancer, are related to people being overweight or obese, being inactive, and/or eating a poor diet (38). Therefore, maintaining a healthy weight, being physically active, and consuming a balanced diet are effective ways a person can lower his or her risk of developing or dying from cancer (see sidebar on **Reduce Your Risk for Cancer Linked to Being Overweight or Obese, Being Inactive, and/or Consuming a Poor Diet**). Exactly how obesity increases a person's risk for cancer is not well understood, but accumulating evidence indicates a critical role for inflammatory immune cells within the fat tissue (53).

Being overweight or obese as an adult increases a person's risk for 14 different types of cancer (see **Figure 6**, p. 31) (55). According to the most recent data available, in 2012, it

Globally,
91 million
children ages 5 to 17 are projected to be obese by 2025 (54).

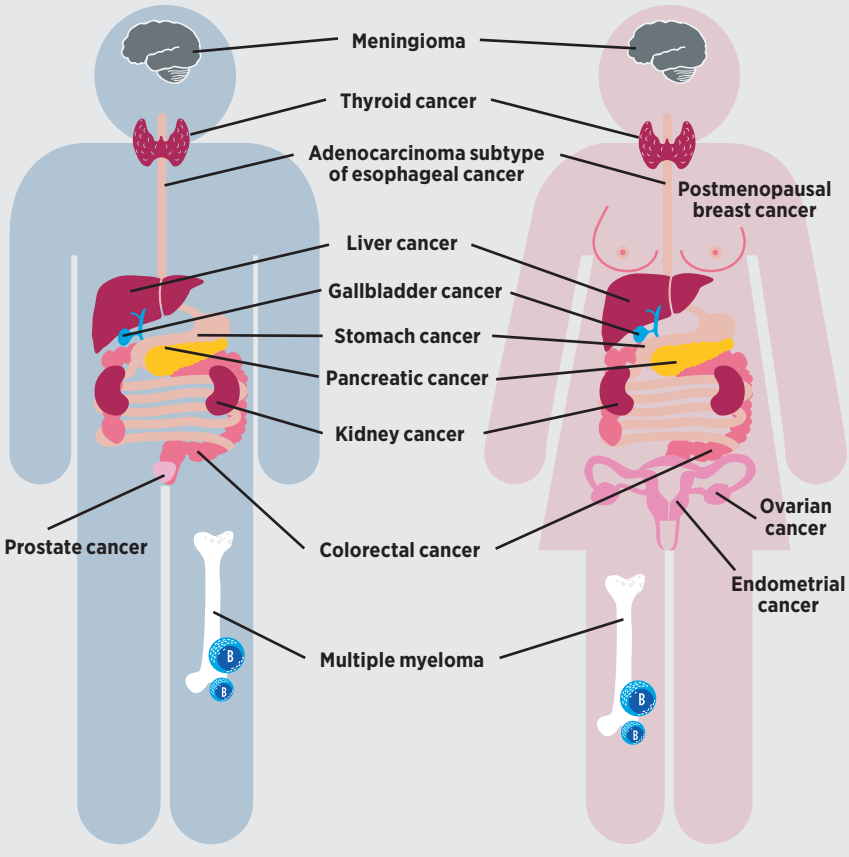
caused about 481,000 new cases worldwide (56). Therefore, it is extremely concerning that in the United States, an estimated, 37 percent of adults and 17 percent of youth are obese, while the annual medical cost of obesity is almost $150 billion (57). In addition, more than 70 percent of high school students do not meet the relevant recommended guidelines for aerobic activity (see sidebar on **Physical Activity Guidelines**, p. 32), and one in four adults age 50 years and older are physically inactive (58-60).

Several steps to promote physical activity for all segments of the U.S. population are outlined in *Step it up! The Surgeon General's Call to Action to Promote Walking and Walkable Communities* and in the U.S. National Physical Activity Plan (38). Nevertheless, concerted efforts by individuals, families, communities, schools, workplaces, institutions, health care professionals, media, industry, government, and multinational bodies are required to implement effective interventions that promote the maintenance of a healthy weight or encourage behavioral modifications

Just **1 or 2 sessions per week** of moderate-intensity physical activity was sufficient to reduce cancer mortality risks (61).

Figure 6

Weighing the Evidence: Cancers Caused by Obesity



Fourteen types of cancer—the adenocarcinoma subtype of esophageal cancer, advanced prostate cancer, meningioma, multiple myeloma, and colorectal, endometrial, gallbladder, kidney, liver, ovarian, pancreatic, stomach, thyroid, and postmenopausal breast cancers—have all been directly linked to being overweight or obese (55).

Figure adapted from (25)

in overweight or obese populations. Furthermore, new approaches to encourage weight loss among overweight or obese individuals need to be evaluated. For example, a recent trial in the United Kingdom reported that a brief, behaviorally informed intervention from physicians led to significant weight loss in patients who were obese (62).

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 (38). One recent policy initiative to help people make better informed food choices and meet the new dietary guidelines is the FDA decision to change the regulatory requirements for the information that manufacturers must provide on nutrition facts labels on food packaging, including the new requirement for information about how much sugar has been added to the food product (38). Another policy that is aimed at reducing obesity is the recent introduction of taxes on sugar-sweetened beverages, which is a major contributor of caloric intake among U.S. youth and adults, in seven local

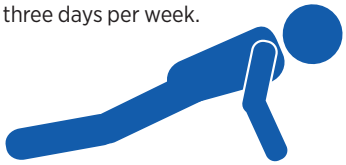
Physical Activity Guidelines

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

For children and adolescents

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

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

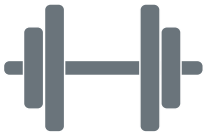


For adults

All adults should avoid inactivity; some physical activity is better than none.

At least 150 minutes per week of moderate-intensity activity such as a brisk walk or 75 minutes per week of vigorous-intensity activity such as running.

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



For specific populations

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

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

Adapted from (1)

jurisdictions within the U.S. (38, 63-65). Ongoing research is needed to evaluate the long-term effects of these policies on consumption, obesity, and obesity-related health outcomes.

Unfortunately, the burden of diet-related disease, including diet-related cancer, is disparately higher in low-income communities and studies show that individuals from the lowest income groups rarely receive weight-loss advice from their health care providers (66). The high cost of fresh produce relative to calorie-dense, nutrient-poor foods is also considered a barrier to healthier eating among those in the lowest-income groups. One statewide initiative designed to address this is Double Up Food Bucks (DUFB) in Michigan, which matches Supplemental Nutrition Assistance Program (SNAP) funds spent at farmers' markets. Uptake of DUFB was initially low, but a brief intervention, explaining the initiative to those eligible, resulted in a fourfold increase in uptake, as well as significant increases in fruit and vegetable consumption in a low-income, racially and ethnically diverse community in Michigan (67).

New public education and policy initiatives, such as DUFB, are important steps toward reducing the burden of cancer caused by being overweight or obese, being inactive, and/or eating a poor diet. More work is needed, however, to better understand the effect of exposure to these risk factors at various stages of life on cancer development. For example, a recent study showed that weight gain of 2.5 kilograms or more during early to middle adulthood (ages 18 to 55) was associated with an increased risk of developing several chronic diseases, including cardiovascular disease, type 2 diabetes, and obesity-related cancers, later in life (68). Although more research is required to confirm these findings, they highlight the importance of maintaining a healthy weight throughout life.

PROTECT SKIN FROM UV EXPOSURE

Exposure to ultraviolet (UV) radiation from the sun or indoor tanning devices can cause genetic mutations and poses a serious threat for the development of all three main types of skin cancer—basal cell carcinoma, squamous cell carcinoma, and melanoma, which is the most deadly form of skin cancer. Thus, one of the most effective ways a person can reduce his or her risk of skin cancer is by practicing sun-safe habits and not using UV indoor tanning devices (see sidebar on **Ways to Protect Your Skin**).

Despite the knowledge that the three main types of skin cancer can be prevented, fewer than 15 percent of men and 30 percent of women use sunscreen regularly on their faces and other exposed skin when outside for more than 1 hour, and one in three adults in the United States reports experiencing at least one sunburn in the past 12 months (30, 69, 70). In addition, 4 percent of U.S. adults report using an indoor UV tanning device at least once in the past 12 months (38).

Over the past few decades, these continued exposures to UV radiation have fueled a steady rise in melanoma incidence in the United States (71). Thus, it is imperative that multicomponent, community-wide public awareness

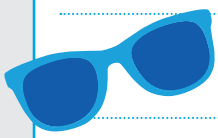
Ways to Protect Your Skin

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

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

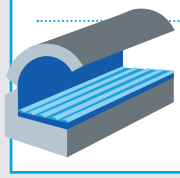
wear clothing that covers your arms and legs; some clothing is designed to provide protection from the sun;

wear a wide-brimmed hat;



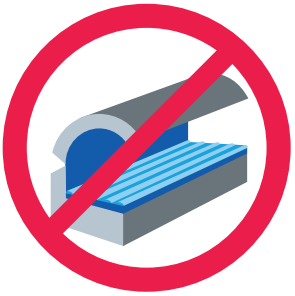
wear wrap-around sunglasses;

apply the recommended amount of a sunscreen that provides protection against UVA and UVB rays and that is rated sun protection factor (SPF) 15 or higher at least every 2 hours and after swimming, sweating, and toweling off; and



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

Adapted from (30)



Seven U.S. states have **no legislation** restricting the use of indoor UV tanning devices: Alaska, Colorado, Iowa, Montana, New Mexico, Oklahoma, and South Dakota.

initiatives as well as restrictive regulatory policies are implemented, to break the current trend and bring down melanoma rates. Based on the findings from a successful public education campaign called "SunSmart" in Australia, the country with the highest skin cancer rates, it is estimated that 230,000 U.S. melanoma cases could be averted between 2020 and 2030 through implementation of nationwide comprehensive skin cancer prevention programs (72, 73). Recently, the Australian campaign has gone digital with the introduction of the "SunSmart" app, which is freely available on Android and Apple devices (73). Whether this effort to personalize and increase access to the message enhances the impact of the campaign needs to be evaluated, but if successful, similar initiatives could be implemented in other countries including the United States.

Reducing indoor tanning also has the potential to reduce melanoma incidence and mortality, as well as the economic

Table 4

Cancer-causing Pathogens

Bacteria

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

Parasites

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

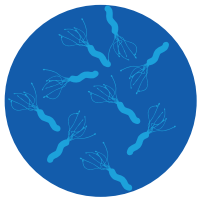
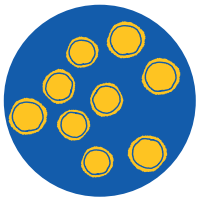
Viruses

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

data from Ref 76

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 	None available	Treatment with a combination of antibiotics and a proton-pump inhibitor can eliminate infection	CDC recommends testing and treatment for people with active or a documented history of gastric or duodenal ulcers, low-grade gastric MALT lymphoma, or early gastric cancer that has been surgically treated
HBV 	• HBV vaccination • Avoid behaviors that can transmit infection (e.g., injection drug use and unsafe sex)	Treatment of those chronically infected with antiviral drugs rarely eliminates infection but does slow virus multiplication; this slows the pace at which liver damage occurs and thereby reduces risk for liver cancer	• Vaccination part of childhood immunization schedule since 1991 • USPSTF recommends screening high-risk individuals—those from countries with high rates of HBV infection, HIV-positive persons, injection drug users, household contacts of HBV-infected individuals, and men who have sex with men—for HBV infection
HCV 	Avoid behaviors that can transmit infection (e.g., injection drug use and unsafe sex)	Treatment with any of several antiviral drugs can eliminate infection	CDC and USPSTF recommend screening those born from 1945 to 1965 for HCV infection
HPV 	• Three FDA-approved vaccines • Practice safe sex, although this may not fully protect against infection	None available	CDC recommends HPV vaccination for: • boys and girls age 11 or 12 • women up to age 26 and men up to age 21 who did not receive the vaccine or complete the course as preteens See sidebar on **updated HPV vaccination recommendations**, p. 36

CDC, Centers for Disease Control and Prevention; HPV, hepatitis B virus; HCV, hepatitis C virus; HPV, human papillomavirus; MALT, mucosa-associated lymphoid tissue; USPSTF, U.S. Preventive Services Task Force. Adapted from (30).

costs related to skin cancers (71, 74). In this regard, in the United States, the FDA has proposed a policy change to ban the use of indoor UV tanning devices by individuals younger than age 18. It is estimated that if this rule were implemented it could avert 62,000 melanoma cases and $343 million in treatment costs (38).

More than 38,000

HPV-associated cancers were diagnosed each year in the United States from 2008 to 2012 (81).

PREVENT INFECTION WITH CANCER-CAUSING PATHOGENS

Persistent infection with a number of pathogens—bacteria, viruses, and parasites that cause disease—increases a person's risk for several types of cancer (see **Table 4**, p. 34). The most recent estimate is that 15 percent of all new cancer cases diagnosed worldwide in 2012 were attributable to pathogens (76), the most common of which were *Helicobacter pylori*, human papillomavirus (HPV), hepatitis B virus (HBV), hepatitis C virus (HCV), and Epstein-Barr virus (EBV) (76). Thus, individuals can significantly lower their risks for certain types of cancer by protecting themselves from infection with cancer-associated pathogens or by obtaining treatment, if available, to eliminate an infection (see sidebar on **Preventing or Eliminating Infection with the Four Main Cancer-causing Pathogens**, p. 35).

Updated HPV Vaccination Recommendations

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

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

Gardasil 9

- Protects against infection with HPV6, 11, 16, 18, 31, 33, 45, 52, and 58.
- FDA approved in 2014 for
  - preventing anal, cervical, vaginal, and vulvar cancers and precancers, as well as genital warts.
  - vaccination of females ages 9 to 26 and males ages 9 to 15.

The U.S. Centers for Disease Control and Prevention (CDC) and the Advisory Committee on Immunization Practices (ACIP) announced updated guidelines for HPV vaccination in October, 2016. According to the new recommendations (82):

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

The updated recommendations are based on recent clinical data showing that, in younger adolescents, two doses of the vaccine trigger an immune response equivalent to that produced by three doses among adolescent girls and young women (83) (see Simplifying the HPV Vaccination Schedule, p. 54).

Although there are strategies available to eliminate, treat, or prevent infection with *Helicobacter pylori*, HBV, HCV, and HPV that can significantly lower an individual's risks for developing an infection-related cancer, it is important to note that these strategies are not effective at treating infection-related cancers once they develop. It is also clear that these strategies are not being used optimally. For example, even though the U.S. Preventive Services Task Force (USPSTF) recommended one-time HCV testing for baby boomers in 2013, data from a 2015 national survey showed that only 10.5 out of 76.2 million eligible candidates reported getting tested (77). Given that infection with HCV is estimated to be responsible for six out of 10 liver cancer cases diagnosed since 2000, the burden of hepatocellular carcinoma could be significantly reduced through more effective implementation of HCV screening and treatment (38, 78).

In addition, the development of strategies to increase uptake of HPV vaccines could have an immense impact on cancer prevention (see sidebar on **Updated HPV Vaccination Recommendations**, p. 36). Research suggests that HPV vaccination could prevent nearly all cases of cervical cancer, as well as many cases of oral and anal cancer, but only 63 percent of girls and less than 50 percent of boys had received at least one dose of HPV vaccine in 2015 (79). This level of uptake is much lower than occurs for other vaccinations received in adolescence (79). Development of comprehensive communications strategies that allow physicians to encourage HPV vaccination with successful implementation are critical to enhance uptake. In this regard, one recent clinical trial showed an increase in HPV vaccine initiation among 11- and 12-year-olds, when health care providers announced that vaccination was due, rather than having a participatory conversation with the family (80).

LIMIT EXPOSURE TO ENVIRONMENTAL RISK FACTORS

There are a number of factors that we may be exposed to in our environment, including environmental pollutants and occupational agents, that can increase a person's risk of cancer (see **Figure 4**, p. 26). For example, radon is a naturally occurring radioactive gas that comes from the breakdown of uranium in soil, rock, and water; it is the second leading cause of lung cancer in the United States (42). Other examples of environmental cancer risk factors include asbestos, lead, radiation, and benzene. Outdoor air pollution is a complex cancer risk factor because it is a mixture of pollutants that vary over space and time as a result of differences in climate and sources.

It is often difficult for people to avoid or reduce their exposure to many environmental cancer risk factors, and not every exposure will inevitably lead to cancer. The intensity and duration of exposure, combined with an individual's biological characteristics, including genetic makeup, determine the chances of developing cancer over his or her lifetime. Therefore, it is imperative that regulatory policies are put in place to ensure that every person lives and works in a safe and healthy environment.

In the United States, policies that help protect people from some of the known environmental cancer risk factors have been in place for several decades. For example, there are numerous policies to help prevent exposure to asbestos, which can cause mesothelioma, an aggressive type of cancer, with few treatment options (84). Despite the existence of regulatory policies, the number of deaths from malignant mesothelioma has been increasing in recent years, particularly among younger populations, which underscores the need for greater efforts to prevent exposure (84). Another important element in studying environmental cancer risk factors is to consider the effect of several factors together, since environmental exposures may occur simultaneously. A recent study from the EPA evaluated the environmental quality index (EQI), a measure of overall environmental exposures, and found a potential increase in overall cancer incidence with decreasing environmental quality (85).

It is important to note that there are considerable disparities in the burden of cancer due to exposure to environmental cancer risk factors (30, 38). These disparities are primarily based on geographic location 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.

45,221

malignant mesothelioma deaths were reported in the United States from 1999 to 2015 (84).

SCREENING FOR CANCER PREVENTION AND EARLY DETECTION

In this section you will learn:

- Research identifying the biological underpinnings of cancer initiation and development has led to screening tests that can be used for cancer prevention and early detection.
- There are five types of cancer for which screening tests have been developed and used in the clinic to screen generally healthy individuals.
- Independent groups of experts rigorously evaluate data on the benefits and potential risks of cancer screening tests before putting forth recommendations about the use of the tests.
- Every person has a unique risk for each type of cancer based on his or her genetic, molecular, cellular, and tissue makeup, as well as his or her lifetime exposures to cancer risk factors.
- Some people are at increased risks for certain cancer types and may need to take measures to reduce the risks.
- There are significant disparities in cancer screening rates among certain segments of the U.S. population.

Most cancers arise and progress as a result of the accumulation of genetic mutations that disrupt the orderly processes controlling the multiplication and life span of normal cells. There are numerous factors that cause cells to acquire genetic mutations (see sidebar on **Sources of Genetic Mutations**, p. 19 and **Figure 4**, p. 26). The identity, order, and speed at which a cell acquires genetic mutations determine whether a given cancer will develop and, if a cancer does develop, the length of time it takes to happen.

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 strategies to detect, if present, precancerous lesions or cancer at an early stage of development (see **Figure 7**, p. 39). If precancerous lesions are found to be present they can be removed before they become cancer, something that is sometimes referred to as cancer interception. Finding cancer early, before it has spread to other parts of the body, makes it more likely that a cancer can be intercepted and a patient treated successfully.

WHAT IS CANCER SCREENING AND HOW IS IT DONE?

Cancer screening 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. It has many benefits, but it can also result in unintended adverse consequences (see sidebar on **Cancer Screening**, p. 40). Thus, population-level use of a cancer screening test must decrease deaths from the screened cancer and provide benefits that outweigh the potential risks. Determining whether broad implementation of a screening test across the population can achieve these two goals requires extensive research and careful analysis of the data generated.

There are five types of cancer for which screening tests have been developed and used in the clinic to screen generally healthy individuals (see sidebar on **Cancers for Which Population-level Screening Has Been or Is Being Performed**, p. 42). Some of these tests can be used to prevent cancer from developing because they detect precancerous changes in a tissue that can be removed before they have a chance to develop into cancer. Others can detect cancer at an early stage of development, when it is more likely that a patient can be treated successfully.

For cancers other than breast, cervical, colorectal, lung, and prostate cancer there has never been population-level use of a screening test for individuals at average risk for disease. Thus, more research is needed to identify biomarkers and

develop imaging technologies that can be used to develop new screening tests and cancer prevention therapeutics, as well as to more precisely identify those for whom current and future cancer screening and cancer prevention therapeutics are beneficial. Two areas of research that show promise in this regard involve expanding our knowledge of the genetic, molecular, and cellular characteristics of precancerous lesions (86, 87), and increasing our understanding of the inherited genetic mutations and variations that increase a person's risk for certain types of cancer (88).

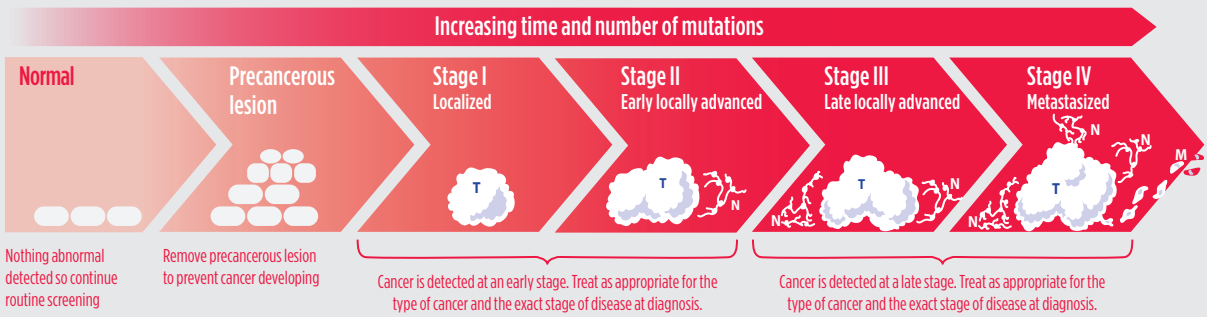
WHO SHOULD BE SCREENED, WHEN SHOULD THEY BE SCREENED, AND WHY?

In the United States, an independent group of experts convened by the Agency for Healthcare Research and Quality of the U.S. Department of Health and Human Services rigorously evaluates data regarding the benefits and potential risks of cancer screening tests to make evidence-based recommendations about the routine use of these tests. These volunteer experts form the U.S. Preventive Services Task Force (USPSTF). The evidence-based USPSTF recommendations fall into several categories, most prominently recommendations for screening certain average-risk individuals at certain intervals, recommendations against screening, and deciding that there is insufficient evidence to make a recommendation (see sidebar on **USPSTF Cancer Screening Recommendations**, p. 41). In addition to considering evidence regarding potential new screening programs, the USPSTF reevaluates existing recommendations as new research becomes available and can revise them if deemed necessary.

Many professional societies also convene panels of experts to meticulously evaluate data regarding the benefits and potential risks of cancer screening tests, and each society has made its own evidence-based recommendations about the use of these tests. Because the representatives on each panel weighing the benefits and potential risks of a given

Figure 7

Cancer Screening: What Can Be Found? What Can Be Done?



Many cancers are progressive in nature. In the example depicted here, a normal cell acquires a genetic mutation that leads to its gaining precancerous characteristics. As the cell multiplies and acquires more genetic mutations, the precancerous lesion becomes increasingly abnormal. Over time, as additional genetic mutations accumulate, the precancerous lesion may evolve into a cancerous lesion (T), then spread to nearby lymph nodes (N), and, as it becomes more advanced, ultimately metastasize (M). When a person is screened for a given cancer there are many different things that can be found and many different outcomes based on the finding. For example, the screening test may show that there is no abnormality present. It may find a precancerous lesion, which can be removed before it develops into a cancerous lesion; in this situation, the screen has led to cancer prevention. It may find a cancer at an early stage of development, stage I or stage II, before it has spread and at a point at which it is more likely that the patient can be treated successfully. It may also find a cancer at a late stage of development, stage III or stage IV, when treatment is less likely to be curative. Removing a precancerous lesion or treating early-stage cancer is sometimes called cancer interception.

Adapted from (30)

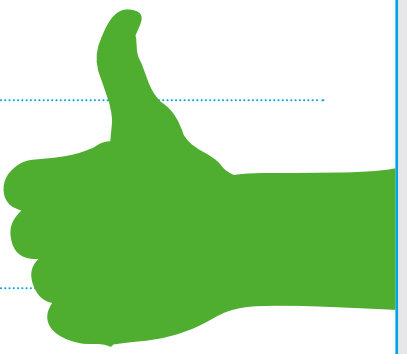
Cancer Screening

Benefits of Screening

Reduced cancer incidence. Screening tests can detect precancerous lesions. Removal of the lesions can reduce, or even eliminate, an individual's risk of developing the screened cancer at that site (see **Figure 7**, p. 39).

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

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

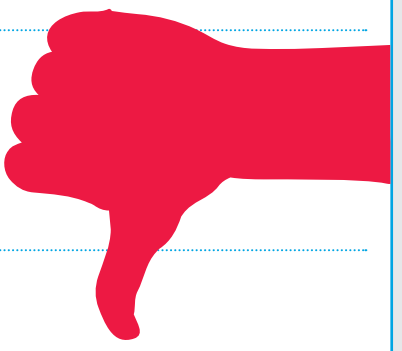


Potential Risks of Screening

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

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

False-positive test results. Not all individuals who have a positive screening test result have the screened cancer. 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 precancers or cancers detected by screening will go on to cause symptoms and threaten life. Overdiagnosis, as this is called, can lead to overtreatment, which may carry its own risks and costs. The rates of overdiagnosis and overtreatment vary among screening tests and will require more longitudinal studies to elucidate and quantify.

Adapted from (1)

cancer screening test are often different, and different groups give more weighting to certain benefits and potential risks than other groups do, this can result in differences in recommendations from distinct groups of experts.

The existence of different cancer screening recommendations can make it challenging for individuals to ascertain which cancers to be screened for and when. Nevertheless, there is more consensus among recommendations than disagreement (see sidebar on **Consensus among Cancer Screening Recommendations**, p. 44). The differences among the recommendations of different groups of experts highlight the areas in which more research is needed to determine more clearly the relative benefits and potential risks of screening, to develop new screening tests that have clearer benefits and/or lower potential risks, or to better identify people for whom the benefits of screening outweigh the potential risks.

Evidence-based cancer screening recommendations that apply to individuals at average risk of disease are only one consideration when a person makes decisions about which cancers he or she should be screened for and when. A person's own unique risks for developing each type of cancer, his or her tolerance of the potential risks of a screening test, and his or her general health are also important considerations. Each person's overall risks are determined by genetic, molecular, cellular, and tissue makeup, as well as by lifetime exposures to cancer risk factors (see **Figure 3**, p. 24). Therefore, every individual should consult with his or her health care practitioner to develop a cancer prevention and early detection plan tailored to his or her personal cancer risks and tolerance of potential screening risks as **Leon Adams** did (see p. 46). These factors can vary over a person's lifetime so it is important that individuals keep up a dialog with their health care practitioner and continually evaluate their cancer screening plans, updating them if necessary. One recent study found that the way in which health care practitioners put forward information can heavily influence whether older adults continue screening, even if it is unlikely to benefit them (89).

Some individuals are at increased risk of certain cancers because they inherited a cancer-predisposing genetic mutation (see **Table 3**, p. 22). If an individual has a family or personal history of cancer and thinks that he or she is at high risk for inheriting such a mutation, he or she should consult a physician and consider genetic testing (see sidebar on **How Do I Know If I Am at High Risk for Developing an Inherited Cancer?**, p. 43). There are genetic tests that individuals can use without a prescription from a physician, but there are many factors to weigh when considering whether to use one of these direct-to-consumer tests. As a result of the complexities of these tests, including the potential for them to detect genetic changes whose association with disease

USPSTF Cancer Screening Recommendations

The U.S. Preventive Services Task Force (USPSTF) rigorously evaluates data regarding the benefits and potential risks of cancer screening tests to make evidence-based recommendations about the routine use of these tests. As of July 31, 2017, the USPSTF had evaluated data and made decisions for 11 types of cancer. Of note, the USPSTF is currently reviewing its recommendations for cervical cancer, ovarian cancer, pancreatic cancer, and prostate cancer screening and may revise them if deemed necessary.

The USPSTF recommends population-level screening of certain individuals for: breast cancer, cervical cancer, colorectal cancer, and lung cancer (see sidebar on **Consensus among Cancer Screening Recommendations**, p. 44, for more details).

The USPSTF recommends against population-level screening of average-risk individuals with no signs or symptoms of: ovarian cancer, pancreatic cancer, testicular cancer, and thyroid cancer.

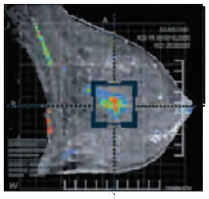
The USPSTF considers there is insufficient evidence to assess the balance of benefits and harms of screening average-risk adults with no signs or symptoms of: bladder cancer, oral cancer, and skin cancer.

For more information about the USPSTF decisions see http://www.uspreventiveservicestaskforce.org

Cancers for Which Population-level Screening Has Been or Is Being Performed

Highlighted here are cancer screening tests that have been used in the clinic, at some time or another, to screen generally healthy individuals. When to use these tests and in whom is discussed elsewhere (see **Who Should Be Screened, When Should They Be Screened, and Why? p. 39).**

BREAST CANCER



Screening mammogram: Uses X-rays to image the breast. The information generated by the procedure can be stored on film (a conventional mammogram) or electronically (a digital mammogram).

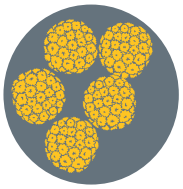
In most cases, the image is 2-dimensional but some machines generate 3-dimensional images in a process called breast tomosynthesis.

Can detect breast cancers that cannot be felt. These cancers can be at any stage of development, but the aim of screening is to find them at the earliest possible stage.

CERVICAL CANCER

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

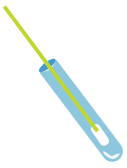
Can detect precancerous or cancerous cervical lesions, but the aim of screening is to find them at the earliest possible stage.



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

Does not directly detect precancerous or cancerous cervical lesions, but identifies people for whom follow-up is recommended.

COLORECTAL CANCER



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

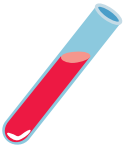
Do not directly detect colorectal precancerous lesions or cancers, but identify people for whom further testing is recommended.

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

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

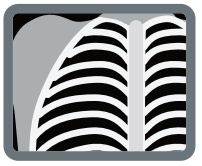
Can detect colorectal precancerous lesions or cancers, but the aim of screening is to find them at the earliest possible stage so that they can be removed.



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

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

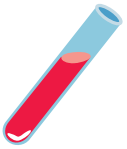
LUNG CANCER



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

Can detect lung cancers that are not causing symptoms. These cancers can be at any stage of development, but the aim of screening is to find them at the earliest possible stage.

PROSTATE CANCER



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

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

Adapted from (30)

risk is unknown (see sidebar on **Interpreting Genetic 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.

Several medical conditions also increase a person's risk for certain types of cancer. For example, individuals who have ulcerative colitis or Crohn's disease are at increased risk for colorectal cancer, although recent research suggests that the increased risk might not be as great as previously estimated (93, 94). Thus, more comprehensive studies are needed to accurately establish the increased risk to allow individuals with these medical conditions to develop optimal cancer prevention and early-detection plans. Ulcerative colitis and Crohn's disease are relatively rare conditions, but much more common medical conditions also increase risk for certain types of cancer. For example, diabetes, which affects 9.3 percent of U.S. adults age 18 or over (95), increases an individual's risk for several types of cancer, including liver, pancreatic, and endometrial cancers (96).

How Do I Know If I Am at High Risk for Developing an Inherited Cancer?

According to the National Cancer Institute, some of the factors to consider are whether, in your family, there is one or more of the following (90):

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

Interpreting Genetic Tests

Genetic testing is a type of medical test that looks for changes, or mutations, in a person's DNA. Some individuals with a family or personal history of cancer decide to undergo genetic testing to determine whether they have inherited a genetic mutation that predisposes them to cancer. Many make this decision in consultation with a health care professional trained in genetics but some decide to use a direct-to-consumer test. Because of the complexities of direct-to-consumer tests, both the FDA and Federal Trade Commission recommend involving a health care professional in any decision to use these tests, as well as to interpret the results.

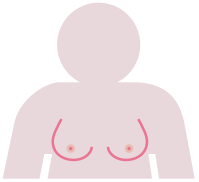
Interpreting the results of genetic tests can be challenging and it is important to remember that not everyone who inherits a cancer-predisposing mutation will develop cancer. One of the challenges is that the effects of a genetic mutation on the risk of developing cancer are not always known. These mutations are often called "variants of unknown significance." Determining whether these variants are inconsequential or important in driving cancer is an area of intensive research investigation. One approach being undertaken involves sharing of genetic test results. By pooling test results and clinical data obtained at institutions around the world to generate large data sets, it should be possible to gain new insight into the frequency and consequences of these variants.

This approach is being used by the BRCA Exchange of the Global Alliance for Genomics and Health to advance our understanding of the genetic basis of breast cancer, ovarian cancer, and other diseases. As of July 31, 2017, the publicly available database contained 18,952 unique BRCA1/2 variants. This should provide an invaluable resource given that it is estimated that BRCA variants of unknown significance occur in 10 percent to 20 percent of BRCA tests (91), which are among the most common genetic tests performed given that mutations in the genes BRCA1 and BRCA2 account for 5 percent to 10 percent of breast cancer cases in U.S. women (92).

For more information on the BRCA Exchange go to: http://brcaexchange.org.

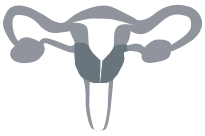
Consensus among Cancer Screening Recommendations

The U.S. Preventive Services Task Force (USPSTF) and many professional societies have evidence-based recommendations about the use of cancer screening tests. Here, we highlight consensus, as of July 31, 2017, among cancer screening 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

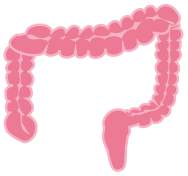
There is consensus among the ACOG, ACS, NCCN, and USPSTF that women ages 50–74 who are at average risk for breast cancer should have regular screening mammograms. However, there is variability about whether this should be done every year or every other year.



CERVICAL CANCER

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

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

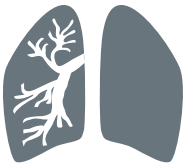


COLORECTAL CANCER

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

- adults ages 50–75 who are at average risk for colorectal cancer should be screened; and
- adults ages 50–75 should consult with their health care providers to choose the test that is right for them.

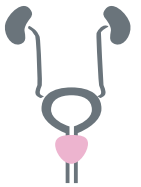
Some professional societies recommend certain approaches over others. The overall message, however, is that using any one of the approved tests is better than not being screened.



LUNG CANCER

There is consensus among the ACS, ACP, and USPSTF that screening with low-dose computed tomography should be limited to adults ages 55–79 who are at high risk for lung cancer because they have smoked at least one pack of cigarettes per day for 30 years, or the equivalent (two packs per day for 15 years, etc.), and who currently smoke or have quit within the past 15 years.

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



PROSTATE CANCER

There is consensus among the ACS, ACP, and AUA that men ages 55–69 who are at average risk for prostate cancer talk to a physician about the benefits and potential harms of PSA testing before deciding if screening is right for them. The USPSTF is finalizing new recommendations and is considering a recommendation that would be aligned with those of the ACS, ACP, and AUA.

Many of the professional societies have additional recommendations that cover people who fall outside the age groups highlighted here and people who are at increased risk for certain cancers, such as those with multiple family members with a given cancer and racial and ethnic minorities.

To find out more about cancer screening recommendations see: ***https://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 (30)

If a person is at increased risk for developing a certain type or types of cancer, he or she should consult with his or her health care practitioner to tailor risk-reducing measures to his or her personal needs. Some people may be able to reduce their risk by modifying their behaviors, for example, by quitting smoking. Others might need to increase their use of certain cancer screening tests or use cancer screening tests that are not recommended for people who are generally healthy. Yet others may consider taking a preventive medicine or having risk-reducing surgery (see **Table 5** and **Supplemental Table 1**, p. 108).

Recent data show that about 10 percent of childhood cancers are associated with specific, inherited genetic mutations. In an effort to facilitate early detection and treatment of these cancers, the AACR convened an international group of leading pediatric cancer experts who have developed and published consensus screening surveillance recommendations for children with the most common cancer predisposition syndromes (97).

As we learn more about the genetic, molecular, and cellular characteristics of precancerous lesions and the biology of cancer, we will be able to develop and implement new strategies that pair this increased understanding with knowledge of an individual's unique cancer risk profile, including his or her genetic makeup at birth, exposures to cancer risk factors, age, and gender. This information will allow us to better tailor cancer prevention and early detection to the individual patient, ushering in a new era of precision cancer prevention (98, 99). Importantly, we must ensure that advances are uniform for all segments of the population, which may prove challenging given that there are currently significant disparities in cancer screening rates among certain segments of the U.S. population (see sidebar on **Disparities in Cancer Screening**).

Table 5

Surgeries for the Prevention of Cancer

Genetic Mutation	Cancer	Technique	Removes
APC	Colon cancer	Colectomy	Colon/large intestine
BRCA1 or BRCA2	Breast and ovarian cancers	Mastectomy and salpingo-oophorectomy	Breasts, and ovaries and fallopian tubes
CDH1	Stomach cancer	Gastrectomy	Stomach
Mutations associated with Lynch syndrome	Colon, endometrial, and ovarian cancers	Colectomy, hysterectomy, and salpingo-oophorectomy	Colon/large intestine, uterus, and ovaries and fallopian tubes
RET	Medullary thyroid cancer	Thyroidectomy	Thyroid

Disparities in Cancer Screening

There are disparities in adherence to United States Preventive Services Task Force (USPSTF) cancer screening recommendations among certain segments of the U.S. population (100, 101). These disparities, which highlight the need for new public policies to increase cancer screening uptake among disadvantaged segments of the U.S. population, include the following:

32% MORE LIKELY Whites are 32 percent more likely to be up to date with colorectal cancer screening than American Indians/Alaska Natives.

MORE THAN 2X Women who have private health insurance are more than twice as likely to be up to date with breast cancer screening than women who are uninsured.

12% MORE LIKELY Straight women are 12 percent more likely to be up to date with cervical cancer screening than gay women.

19% MORE LIKELY Women in the highest income bracket are 19 percent more likely to be up to date with cervical cancer screening than women in the lowest income bracket.

31% MORE LIKELY Colorectal cancer screening uptake varies by U.S. state, with those in Massachusetts 31 percent more likely to be up to date with screening than those in Wyoming.

2X Foreign-born women in the U.S. are twice as likely to have never had a mammogram than U.S.-born women.

LEON ADAMS
Age 65
Philadelphia, Pennsylvania

HOPING TO INCREASE AWARENESS OF CANCER

AFTER A PROSTATE CANCER DIAGNOSIS

© AACR/Vera LaMarche

my experiences with family and friends to help them as they make decisions about their health care.

I knew about the statistics of African-American men and prostate cancer. So, after talking with my primary care doctor, I began regular PSA screening for prostate cancer several years ago. A test in 2011 showed high levels of PSA and I was referred to a urologist, but a biopsy revealed that I did not have prostate cancer.

I feel good after the surgery, but it has left me with some incontinence. I think it happened because my surgery took place sooner than expected due to a cancellation. This meant I did not have as much time before surgery to do the Kegel exercises they recommend to strengthen the pelvic area and decrease the chance of side effects after surgery.

Since my diagnosis, I've talked with family and friends about what I have been going through. I've learned that my grandfather had prostate cancer back in the 1960s and that one of my brothers had the disease in 2006. I've also been able to help a second brother, who was diagnosed with prostate cancer not long after me, navigate treatment decisions and give him an idea of what to expect.

> " I hope that by telling my story I can raise awareness of cancer, in particular prostate cancer, and the need to **be proactive about your health.** "

I was diagnosed with prostate cancer in early 2017. I am lucky that the disease was caught before it had spread outside the prostate and surgery is the only treatment I have needed so far. Since my diagnosis, I've realized that there is a need for increased awareness about cancer in the community and I've been sharing

After several years of tests showing low levels of PSA, I chose not to be screened in 2015. Fortunately, I did not skip the test at the end of 2016 because it showed a PSA level of 13; normal is less than 4. I returned to the urologist who did a digital rectal exam and a biopsy, which showed prostate cancer.

Several scans, including a bone scan, showed that the cancer had not spread beyond the prostate. I had several treatment options to choose from, including radiation or surgery. I did some research on the options and talked with a radiologist who said that I would need 8 weeks of radiation therapy. That seemed like a long course of treatment to me and I was also concerned that if I chose radiotherapy and the cancer returned later I might not recover as easily as I would at 65 from surgery. Ultimately, I chose robotic surgery because it offered a shorter recovery time than open surgery.

I had the surgery in April 2017 and my PSA results after that showed that the PSA level is below 0.1, so I will be monitored, but I'm not having any more treatment at this point.

Given that my outlook would not be as good as it is now if I had not gone for my PSA test in 2016, that we have a family history of prostate cancer, and that the statistics for African-American men and prostate cancer are not good, I've also been encouraging the men in my family as well as friends who are getting older to talk with their doctors about PSA screening.

Many men think they are invincible and are reluctant to go to a doctor for annual checkups even if they feel that they might have a problem. I hope that by telling my story I can raise awareness of cancer, in particular prostate cancer, and the need to be proactive about your health. It is better to prevent cancer from developing or catch it early than to find that you have metastatic disease. ■

HARNESSING RESEARCH DISCOVERIES TO SAVE LIVES

In this section you will learn:

- Progress against cancer is driven by research discoveries.
- From August 1, 2016, to July 31, 2017, the FDA approved nine new therapeutics for treating certain types of cancer.
- During the same period, the FDA authorized new uses for eight previously approved anticancer therapeutics.
- The number of types of cancer for which immunotherapy is an approved treatment option is increasing rapidly.
- Cancer genomics research is the foundation for novel clinical trials designed to accelerate the pace at which new therapeutics are approved for patient care.
- Identifying ways to help survivors meet the many challenges they face after a cancer diagnosis is an area of intensive research investigation.

The dedicated efforts of individuals working throughout the cycle of biomedical research have improved and saved lives around the world by driving progress across the continuum of clinical cancer care (see **Figure 8**, p. 49).

BIOMEDICAL RESEARCH

Biomedical research is an iterative cycle, building on prior knowledge, with one discovery influencing the next (see **Figure 8**, p. 49). In recent years, the cycle has become increasingly efficient as the pace of discovery has increased and new disciplines have been integrated. As a result of these changes, the rate at which research discoveries are being converted to lifesaving advances across the continuum of clinical cancer care has been accelerating. To maintain this momentum it is imperative that we better support investigators throughout their careers, but especially those early in their careers (see sidebar on **Supporting Early-Career Investigators**, p. 50) (see **Developing and Training the Cancer Workforce of Tomorrow**, p. 101).

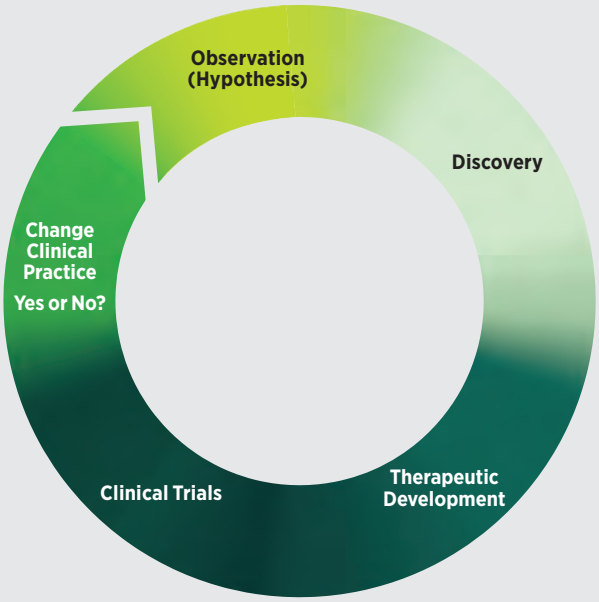
In short, the biomedical research cycle is set in motion when discoveries with the potential to affect the practice of medicine and public health are made in any area of biomedical research, including basic research, population research, clinical research, and clinical practice. The discoveries lead to questions, or hypotheses, that are tested by researchers performing experiments in a wide range of models that mimic what happens in healthy and diseased conditions. These models range from single cells and tissues from animals and/or humans to whole animals, individuals, and entire populations. The results from these experiments can lead to the identification of a potential therapeutic target, predictive biomarkers, or preventive intervention, or they can feed backward in the cycle by providing new discoveries that lead to more hypotheses.

After a potential therapeutic target is identified, it takes many more years of research before a candidate therapeutic is developed and ready for testing in clinical trials (see sidebar on **Therapeutic Development**, p. 51). During this time, candidate therapeutics are rigorously tested to identify an appropriate dose and schedule, as well as any potential toxicity.

Clinical trials are a central part of the biomedical research cycle that ensure that research discoveries ultimately reach the patients who need them the most as quickly and safely as possible. Before most potential new diagnostic, preventive, or therapeutic products can be approved by the FDA and used as part of patient care, their safety and efficacy 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.

Figure 8

The Biomedical Research Cycle



Results from any type of research can fuel biomedical research 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. 51). Before entering clinical testing, potential therapeutics are subjected to preclinical testing to identify any toxicities and help determine initial dosing. Clinical testing is a multiphase process aimed at demonstrating the safety and efficacy of a potential therapeutic (see **Figure 9**, p. 52). If a therapeutic is safe and effective and is approved for use by the U.S. Food and Drug Administration (FDA), it will enter into clinical practice, where it can transform the lives of patients. Importantly, observations made during the routine use of a new therapeutic can feed back into the biomedical research cycle and further enhance the use of that therapeutic 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 biomedical research cycle to spur future research efforts. Because the cycle is iterative, it is constantly building on prior knowledge, and research undertaken during any part of the cycle continually powers new observations.

Figure adapted from (25)

In oncology, treatment clinical trials have traditionally been done in three successive phases (see **Figure 9**, p. 52). This approach has yielded numerous advances in patient care. 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 biggest barriers to rapid translation of scientific knowledge into clinical advances. Other challenges include low participation in clinical trials by adolescents and adults with cancer and a lack of diversity among clinical trial participants, in particular adult clinical trial participants (102–105) (see sidebar on **Disparities in Clinical Trial Participation**, p. 53).

Over the past three decades, the FDA has implemented several changes that have altered how clinical trials can be conducted and reviewed in an effort to reduce the length of time it takes to obtain a clear result from a clinical trial, including developing four evidence-based strategies to expedite assessment of therapeutics for life-threatening diseases such as cancer. An increasing number of therapeutics are being approved by the FDA using these review strategies (108). For example, eight of the new anticancer therapeutics approved by the FDA during the 12 months spanning this report were approved using one or more of the expedited review strategies.

In addition, research-driven advances in our understanding of cancer biology, in particular the genetic mutations that underpin cancer initiation and growth (see **Cancer Development: Influences inside the Cell**, p. 18), are enabling researchers, regulators, and the pharmaceutical industry to develop new ways of designing and conducting clinical trials, including the emergence of adaptive and seamless clinical trial designs (109, 110). The new approaches aim to streamline the development of new anticancer therapeutics by matching the right therapeutics with the right patients earlier. These approaches can reduce the number of patients who need to be enrolled in clinical trials before it is determined whether or not the therapeutic being evaluated is safe and effective. They can also decrease the length of time it takes for a new anticancer therapeutic to be tested and made available to patients.

In some clinical trials, the cancer-driving genomic alterations and not the anatomic site of the original cancer are being used to identify the patients most likely to benefit from an investigational anticancer therapeutic. If successful, these clinical trials, which are called "basket" trials, have the potential to lead to FDA approvals that are agnostic of the site of cancer origin (see **Figure 10**, p. 52). The first such FDA

approval occurred in May 2017 (see **Releasing the Brakes on the Immune System**, p. 72). The approval came after regulatory review of data from several basket-like studies using two of the expedited-review strategies, highlighting how regulatory and scientific advances are being used together to drive progress against cancer. Another example of a basket trial that has yielded promising early results involves the testing of a molecularly targeted therapeutic called larotrectinib in adult and pediatric patients with any type of cancer characterized by the presence of genetic alterations called TRK fusions (111).

"Umbrella" trials are a second type of genomics-based clinical trial that are becoming increasingly common (see **Figure 10**, p. 52). In contrast to the tumor site–agnostic basket trials, umbrella trials test multiple therapeutics across multiple genetic mutations on a group of patients who all have cancer arising in the same anatomic site.

Basket and umbrella trials are likely to become even more common in the future as researchers identify ways to better leverage the enormous amount of genomic data that has accumulated in recent years (see **Looking to the Future**, p. 89).

Supporting Early-Career Investigators

A strong and diverse pipeline of early-career investigators is vital if we are to continue to accelerate the pace of progress against cancer. To cultivate this pipeline we need robust, sustained, and predictable funding increases for the National Institutes of Health, as well as federal, state, philanthropic, and private funding programs. In this regard, the American Association for Cancer Research (AACR) recently launched the AACR NextGen Grants for Transformative Cancer Research with support from Bayer, the Breast Cancer Research Foundation, Incyte Corporation, and Takeda Oncology. Through this program the AACR is helping:

Kivanç Birsoy, PhD, identify how cell nutrients can be targeted for therapy for hard-to-treat cancers;

Sidi Chen, PhD, develop new ways to identify the genes that fuel liver cancer growth and response to treatment;

Hani Goodarzi, PhD, investigate how certain RNA structures can influence colon cancer progression and metastasis (see sidebar on **Genetic and Epigenetic Control of Cell Function**, p. 20);

Andrew C. Hsieh, MD, use multidisciplinary approaches to enhance our understanding of the complex cellular processes that lead to the production of cancer-driving proteins;

Sophia Y. Lunt, PhD, elucidate how pancreatic cancer cells use energy to support tumor growth and metastasis;

Costas Andreas Lyssiotis, PhD, determine how cells in the tumor microenvironment communicate with pancreatic cancer cells and promote their survival;

Paul A. Northcott, PhD, deepen our understanding of the molecular basis of recurrent childhood medulloblastoma;

Nikhil Wagle, MD, improve our understanding of why breast cancer cells become resistant to molecularly targeted therapeutics that block the function of CDK4/6 proteins (see **Keeping Breast Cancer Cells at Bay**, p. 64).

For more information about the research being conducted by these early-career investigators see **www.AACR.org/Funding/PAGES/NEXTGEN-GRANT-RECIPIENTS.ASPX**

Therapeutic Development

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

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

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

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

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

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

Adapted from (1)

Figure 9

Phases of Clinical Trials

Clinical trials evaluating potential new anticancer therapeutics have traditionally been done in three successive phases, each with an increasing number of patients. Phase I studies are designed to determine the optimal dose of an investigational 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 regulators 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.

Figure 10

Genomically Informed Clinical Trials

A major use of genomics in clinical research is in the design and execution of novel types of clinical trials. Two such types of trials are basket and umbrella trials. In the basket trial depicted here, one drug is being tested against a particular genetic mutation (green dots) across liver, lung, bone, colon, and stomach cancers. In the umbrella trial illustrated here, three different drugs are being tested against multiple genetic mutations (yellow, green, blue, and red dots) within lung cancer.

Figure adapted from (1)

For example, a recent study highlighted the potential for international data-sharing initiatives to facilitate the design of umbrella trials and to identify those patients most likely to be eligible for such trials (112).

As discussed above (see **Cancer Development: Integrating Our Knowledge**, p. 23), research has shown that tumor genomics is not the only factor influencing cancer initiation, development, and progression. Factors such as a person's genome, disease presentation, gender, exposures, lifestyle, and microbiome also play a role (see **Figure 3**, p. 24). We are also beginning to learn that these factors may affect a person's response to a particular treatment, although much more research is needed in this area. For example, a number of studies have shown that the bacterial species in the intestinal microbiota—the microbes that naturally colonize

Disparities in Clinical Trial Participation

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

The elderly (age 65 or older) accounted for about two-thirds of patients with breast, lung, colorectal, and prostate cancer, but only one-third of participants in clinical trials testing treatments for these four types of cancer in one recent study (104).

African-Americans account for about 20 percent of new multiple myeloma cases but just 10 percent of the participants involved in the clinical trials testing daratumumab (Darzalex) (105, 106).

Why Do They Exist?

As with disparities in cancer burden (see sidebar on U.S. Cancer Health Disparities, p. 16), there are many complex and interrelated factors that contribute to disparities in clinical trial participation (103-107). The factors may include, but are not limited to, differences or inequalities in:

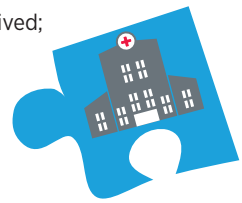
health insurance status;

eligibility criteria;

cultural beliefs; and

social and economic status;

site at which cancer care is received;



health literacy.

Given that a significant proportion of the U.S. population falls into one or more risk categories, it is important that research into these issues continues. Only with new insights will we develop and implement interventions that will ensure that participants in cancer treatment clinical trials appropriately represent all the people who will use the agents if they are approved.

The proportion of people with cancer who participate in a clinical trial varies by age. It is estimated that clinical trial participation is (102):

about 50%

among children younger than 15;

<2%

among adolescents and young adults (ages 15 to 39); and

<5 %

among adults older than 39.

the intestines—of mice influences the anticancer efficacy of cytotoxic chemotherapeutics and immunotherapeutics (113, 114). Recent data suggest that the diversity of the intestinal microbiota may also influence the efficacy of immunotherapeutics in patients with melanoma (115) but much more research is needed in this area.

PROGRESS ACROSS THE CLINICAL CANCER CARE CONTINUUM

The translation of research discoveries to new medical products for cancer prevention, detection, diagnosis, treatment, and care is not the end of a linear research process. Rather, it is an integral part of the biomedical research cycle because observations made during the routine use of new medical products can be used to further enhance the use of those products, to accelerate the pace at which similar products are developed, or to stimulate the development of new, more effective products (see **Figure 8**, p. 49).

The following discussion focuses primarily on the new FDA-approved medical products, which are improving lives by having an effect across the continuum of clinical cancer care. However, it is important to note that they are used alongside medical products already in clinical use. For example, most patients with cancer are treated with a combination of surgery, radiation, chemotherapy (including both cytotoxic chemotherapeutics and molecularly targeted therapeutics), and/or immunotherapy (see **Supplemental Table 2**, p. 109, and **Supplemental Table 3**, p. 112).

Cancer Prevention, Detection, and Diagnosis

Preventing cancer from developing and, if cancer develops, detecting it at the earliest stage possible are the most effective ways to reduce the burden of cancer. The development of new and better approaches to cancer prevention and early detection have been spurred by research that enhanced our knowledge of the causes, timing, sequence, and frequency of the genetic, molecular, and cellular changes that drive cancer initiation and development.

Simplifying the HPV Vaccination Schedule

Research has shown that almost all cases of cervical cancer, as well as many cases of vulvar, vaginal, penile, anal, and oropharyngeal cancers, in the United States are caused by persistent infection, at the site at which the cancer arises, with certain strains of HPV (see **Prevent Infection with Cancer-causing Pathogens**, p. 36). This knowledge led to the development and FDA approval of three vaccines that protect against infection with some of the cancer-causing strains of HPV by triggering long-lasting immune responses against these strains: Cervarix, Gardasil, and Gardasil 9.

Until October 2016, the CDC recommended that individuals receive three doses of any of the HPV vaccines. After reviewing new research showing that people who received two doses of vaccine had immune responses against HPV that were equivalent to those seen in people who received three doses, the FDA approved a two-dose series of Gardasil 9 for vaccination of children ages 9 to 14 in October 2016 (116). Shortly after, the CDC revised its HPV vaccine recommendations such that it recommends that children ages 11 and 12 receive two doses of HPV vaccine at least six months apart (see sidebar on **Updated HPV Vaccination Recommendations**, p. 36).

HPV vaccine uptake has been very low compared with the uptake of other vaccines given in childhood and adolescence (79). Thus, it is hoped that the research-driven change in the HPV vaccination schedule will increase uptake of the potentially lifesaving vaccine among children because it will mean fewer visits to the doctor.

Enhancing Cancer Detection and Diagnosis with Technology

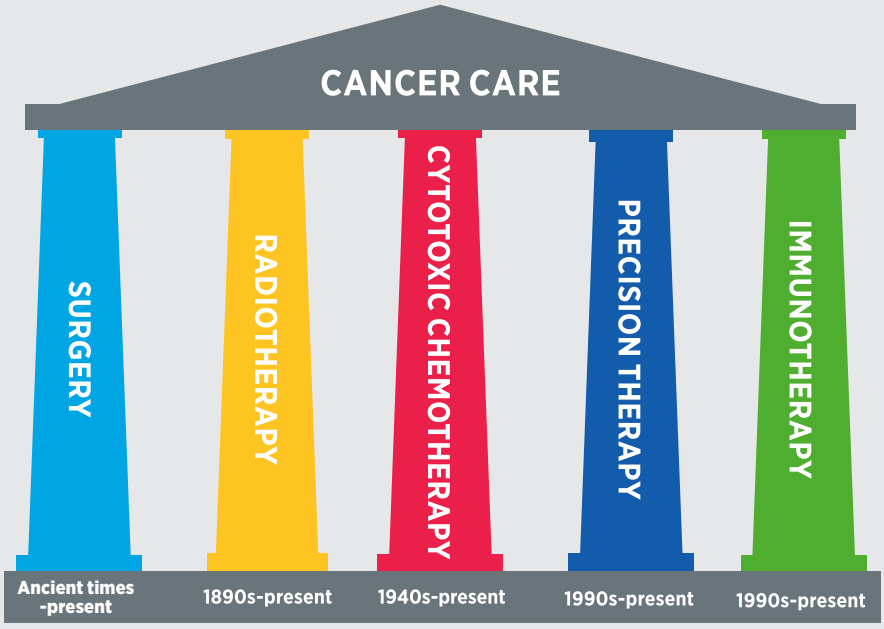
Technological advances are driving the development of new medical products to help better detect and diagnose cancer. One such medical product recently cleared by the FDA is LungVision, an imaging system that is designed to enhance localization and biopsy of early-stage lung lesions during bronchoscopic procedures by allowing physicians to plan, visualize, and track endobronchial tools and radiolucent lesions in real time.

In addition, in March 2017, the FDA approved PowerLook Tomo Detection, a computer-aided detection system designed to increase the efficiency with which radiologists read breast tomosynthesis, or three-dimensional mammography exams. Three-dimensional mammography is a relatively recently introduced approach to breast cancer screening that has been shown to detect more breast cancers than two-dimensional mammography but also to result in an increased percentage of false-positive results (117). Many more images are generated during a three-dimensional mammography exam than during a two-dimensional mammography exam. The new system automatically analyses each image and identifies suspicious areas, then blends these with the image to provide radiologists with a single enhanced image. The enhanced image assists radiologists in identifying suspicious areas and directs them to the appropriate three-dimensional image that they can view to confirm or dismiss the finding.

An important step in diagnosing a suspected tissue abnormality as cancer is pathology testing. This involves a pathologist viewing a slide on which there is a slice of the abnormal tissue, obtained through tissue biopsy or during surgery, under a conventional light microscope to determine the size, shape, and appearance of the tissue and the cells. Technological advances led to the development of a digital pathology system called IntelliSite Pathology Solution, which was approved by the FDA in April 2017. The system is comprised of an ultrafast pathology slide scanner, an image management system, and a display. It is supported by advanced software tools to manage the scanning, storage, presentation, reviewing, and sharing of information. The goal of IntelliSite Pathology Solution is to make the process of pathology testing more efficient and collaborative to increase the accuracy of the resulting diagnosis, thereby improving patient care.

Figure 11

The Pillars of Cancer Care



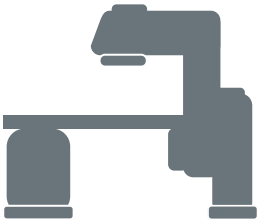
Physicians often refer to the "pillars" of cancer treatment. For thousands of years, there was one treatment pillar: surgery. In 1896, a second pillar, radiotherapy, was added. The foundations for the third treatment pillar, cytotoxic chemotherapy, were laid in the early 1940s when a derivative of nitrogen mustard was explored as a treatment for lymphoma. These three pillars—surgery, radiation, and cytotoxic chemotherapy—continue to be the mainstays of cancer care. However, in the late 1990s, the first precision therapeutics were introduced, leading to the fourth pillar, precision therapy, which continues to grow. Likewise, the late 1990s laid the groundwork for the fifth treatment pillar, immunotherapy. The number of anticancer therapeutics that form the most recent pillars of cancer care has increased dramatically in the past 5 years.

Figure adapted from (25)

Treatment with Surgery, Radiotherapy, and Cytotoxic Chemotherapy

As research has enhanced our understanding of the genetic, molecular, and cellular changes that underpin cancer biology, we have been able to develop an increasing number of therapeutics that more precisely target specific molecules involved in the development and progression of cancer than do the treatments that have been the mainstay of cancer care for decades.

Molecularly targeted therapeutics tend to be more effective and less toxic than two of the long-standing pillars of cancer treatment—radiotherapy and cytotoxic chemotherapy (see **Figure 11**, p. 55). However, not all patients with cancer are treated with molecularly targeted therapeutics. For some patients, this might be because there is no appropriate molecularly targeted therapeutic available. For others, it may be that surgery, radiotherapy, and/or cytotoxic chemotherapy are the best treatment options, as they were for **Congressman Jamie Raskin** (see p. 58) seven years ago. Whatever the reason, the reality is that these traditional therapeutic modalities form the foundation of treatment for almost all patients with cancer, including those for whom molecularly targeted therapeutics and immunotherapeutics are appropriate.



About 50%

of U.S. cancer patients have radiotherapy to shrink or eliminate tumors or to prevent local recurrence (118).

Improving Outcomes by Combining Existing Treatments

Even though much emphasis is put on developing new, more effective anticancer treatments, a large body of researchers are working to identify new ways to combine the treatments that we already have to improve survival and quality of life for patients.

One recent example of a new combination of existing treatments shown in a phase III clinical trial to substantially improve survival for patients with biliary tract cancer is the addition of treatment with the cytotoxic chemotherapeutic capecitabine after they have had surgery (119). Biliary tract cancer, which include cancers of the bile duct and gallbladder, is a rare type of cancer. It is also a type of cancer for which we have made little progress in recent years. In fact, the 5-year relative survival rate is less than 10 percent among the 20 percent of patients who have tumors that are suitable for surgical removal. In the clinical trial, treating patients whose biliary tract cancer had been completely removed by surgery with capecitabine improved survival by more than a year compared with surgery alone.

Another example of a new combination of existing treatments recently found in a clinical trial to improve outcomes for patients is the addition of the immunotherapeutic pembrolizumab (Keytruda) to treatment with the standard cytotoxic chemotherapeutics pemetrexed and carboplatin for the initial treatment of patients with advanced non–small cell lung cancer (NSCLC) (120). Data from the clinical trial showed that adding pembrolizumab to carboplatin and pemetrexed treatment increased the number of patients who had their tumors shrink. It also extended the amount of time until disease progression. Even though longer follow-up of these patients is needed to determine whether this new combination also improves survival, the promising early results led the FDA to approve pembrolizumab for use in this way in May 2017.

A third example of a new combination of existing treatments recently shown to improve outcomes for patients is the addition of the immunotherapeutic daratumumab (Darzalex) to two standard treatments for multiple myeloma, lenalidomide (Revlimid) and dexamethasone, and bortezomib (Velcade) and dexamethasone. In clinical trials, adding daratumumab to these treatments significantly increased the amount of time until disease progression (121, 122). This led to a November 2016 FDA approval of daratumumab for use in combination with lenalidomide and dexamethasone, or bortezomib and dexamethasone, for treating patients with multiple myeloma whose disease has progressed after at least one prior therapy.

Reducing the Adverse Effects of Surgery

For many patients with cancer, surgery is a foundation of their treatment (118). Until 25 years ago, open surgery, whereby the surgeon makes one large cut to remove the tumor, some healthy tissue, and maybe some nearby lymph nodes, was the only approach to cancer surgery. Since then, a number of advances, including the introduction of minimally invasive laparoscopic surgery for some types

of cancer, have helped reduce the morbidity of surgery (123). This reduction in postsurgery complications has led to improved patient quality of life and increased ability to receive subsequent therapies.

Another recent advance was shown to have reduced the number of women with breast cancer who undergo additional surgery after initial lumpectomy (124). For many women diagnosed with early-stage breast cancer, the initial treatment is a lumpectomy—surgery to remove a breast tumor and a small amount of normal tissue around it that leaves most of the breast skin and tissue in place. However, more than 20 percent of patients require a second surgery after a lumpectomy because postsurgery analysis of the removed tumor shows an inadequate margin of normal tissue around the tumor, leaving open the possibility that not all of the tumor was removed. A recent study showed that since the Society of Surgical Oncology and the American Society of Radiation Oncology put forth a new recommendation about how to establish adequate margins of normal tissue around breast tumors removed during a lumpectomy, rates of reoperation after initial lumpectomy for breast cancer have significantly declined (124).

To help surgeons visualize gliomas and ensure more complete removal of the tumor, the FDA approved a new imaging agent called aminolevulinic acid hydrochloride (Gleolan) in June 2017. Gliomas are the most common type of cancer arising in the brain. Many patients with glioma are treated with surgery with the goal of removing as much of the cancer as possible without damaging adjacent healthy brain tissue. Surgery can be very challenging, especially for high-grade cancers that are invasive and for cancers in certain locations in the brain. The approval came after several studies showed that aminolevulinic acid hydrochloride was a safe and effective way to visualize gliomas and more completely remove them during surgery, something that has been linked in other studies to improved patient outcomes (125).

Tailoring Radiotherapy: Less Is Sometimes More

Radiotherapy is a mainstay of cancer care (see sidebar on **Using Radiation in Cancer Care**, p. 60). However, it can have long-term adverse effects on patients. Thus, physicians are looking to tailor each patient's radiotherapy to be only as aggressive as is necessary for it to be effective by moving away from a one-size-fits-all approach to one in which treatment decisions are based on a more complete understanding of the biology of the patient's tumor and the individual's physiological characteristics and needs.

Children with cancers of the central nervous system, which consists of the brain and spinal cord, are particularly vulnerable to the late effects of radiotherapy. Thus, researchers have been looking for genetic, molecular, or cellular markers that can identify certain groups of children with cancers of the central nervous system who can be spared radiotherapy without compromising treatment outcomes. Spurred by advances in our understanding of the biology of medulloblastoma, the most common malignant brain tumor in children, researchers recently reported that in a phase III clinical trial they had identified a subgroup of young children with medulloblastoma who might be able to forgo radiotherapy to the brain without it affecting their chances of survival (126, 127). These results are highly promising, but need to be confirmed in additional studies before they can result in changes in the treatment of children with medulloblastoma.

26%

of all childhood cancers are central nervous system cancers (2).

Radiotherapy is often used to reduce or control symptoms of cancer. For example, radiotherapy is often used to relieve the problems caused by metastatic tumors pressing against the spinal cord. These tumors, which can be in or near to the spine, can cause pain in the back and neck; numbness or pins and needles in the toes, fingers, and buttocks; unsteadiness on the feet; and bladder or bowel problems. Results from a phase III clinical trial were recently reported to show that a single radiation treatment was as effective at keeping patients with a short life expectancy mobile as five radiation treatments over five days and did not significantly reduce median survival time (128). Reducing the number of treatments, and therefore reducing the number of hospital visits, has the potential to help improve the quality of life for these patients who have short life expectancy.

Treatment with Molecularly Targeted Therapeutics

The discovery that most cancers arise as a result of the accumulation of genetic mutations within cells (see **Comprehending Cancer Development**, p. 18), coupled with advances in biology, chemistry, physics, and technology,

continued on ***p. 61***

THE HONORABLE JAMIE RASKIN
U.S. Representative for Maryland's 8th Congressional District
Age 54

SURVIVING COLORECTAL CANCER

AND WORKING TO IMPROVE THE HEALTH OF THE NATION

I was diagnosed with colorectal cancer in 2010. It was an excruciatingly difficult experience for me and my family. But we were fortunate, I was treated by some fantastic doctors and nurses who saved my life. The experience was also a hard-won political epiphany and I am passionate about supporting legislation that increases access to health care and promotes investment in biomedical research and health innovation.

At the start of 2010, life was going smoothly. I had a great family life

© AACR/Karen Sayre

and two jobs that I loved, I was a professor in constitutional law and a state senator. As Susan Sontag put it in *Illness as Metaphor*, when she said that everyone is born with two passports—one for the kingdom of the well and one for the kingdom of the sick—I was using my passport for the land of the living and the healthy.

By the middle of the year, I was using my passport for the sick and the dying.

It all started when I went to the doctor because I was experiencing reflux symptoms. He recommended that I have an endoscopy and then said, "While you are there why don't you have a colonoscopy too." So, I did.

I knew there was something wrong as soon as I woke up from the procedures because there were nurses and doctors all around my bed. They told me they had seen nothing unusual during the endoscopy but that the colonoscopy had revealed a problem. There was mass the size of a walnut in my colon. They didn't know immediately that it was cancer but several days later test results confirmed that it was.

At that point, it was off to the races. I began six weeks of daily radiotherapy and chemotherapy, which was highly effective at shrinking the tumor. Then I had a long but successful surgery to remove the tumor.

My final treatment was another eight cycles of chemotherapy, which the doctors recommended because the cancer had spread to some nearby lymph nodes.

The entire course of my treatment was grueling, especially the surgery, but my family helped me through it. I did take a semester off from teaching but I continued my work in the State Senate. In fact, my floor leadership on marriage equality and repeal of the death penalty gave me something positive to focus on rather than my health.

Since the end of my treatment I've been monitored closely but there has been no sign of recurrence of cancer and I consider myself to be cured but still vigilant. I've also become more determined than ever to increase access to health care. It was hard enough for someone like me, who has great health insurance, to deal with my diagnosis, I cannot imagine how devastating it must be for those who have no health insurance.

One piece of legislation that I am cosponsoring with Congressman Charlie Dent (R-Pa) and Congressman Donald Payne, Jr. (D-NJ), the "Removing Barriers to Colorectal Cancer Screening Act of 2017," aims to eliminate costs for all Medicare beneficiaries receiving a screening colonoscopy, even those who have a polyp removed during the procedure. Currently, if a polyp is discovered and removed during a screening colonoscopy, Medicare beneficiaries are required to pay the coinsurance. Eliminating the possibility that unexpected costs will arise during screening should increase the number of people who get screened, which is vital for early detection and improved survival.

My experience has also strengthened my resolve to make sure that the National Institutes of Health (NIH) gets the investments it needs to keep funding the researchers who are making breakthroughs against diseases like cancer. These diseases affect all of us in some way. So, I'm going to stand up strong and defend deep federal investment in the NIH. It is, after all, an investment in the lives of people all over the country. ■

" My experience [with colorectal cancer] has also strengthened my resolve to make sure that the National Institutes of Health (NIH) gets the investments it needs to keep **funding the researchers who are making breakthroughs against diseases like cancer.** "

Using Radiation in Cancer Care

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

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

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 completely eliminate a cancer, particularly small cancers, as well as locally advanced cancers as part of combination therapy.

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

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

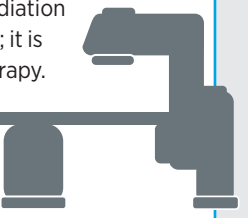
Palliative radiotherapy is used to reduce or control symptoms of disease when cure by another method is not possible.

TYPES OF RADIOTHERAPY

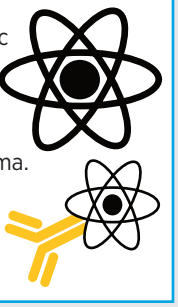
Particle therapy uses protons or carbon ions rather than X-rays as the source of energy. In contrast to X-rays that pass though the body, losing energy and causing damage to the noncancerous tissues through which they pass, these heavier particles deposit most of their energy in the target. In this manner, particle therapy can deliver higher doses with less damage to surrounding tissue. Although of great interest, proton facilities are much more expensive than traditional facilities and the overall benefit to the patient is still being determined.

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

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



Radioisotope therapy involves systemic ingestion or infusion of radioisotopes, for example, iodine-131 to treat thyroid cancer or yttrium-90 ibritumomab (Zevalin) to treat non-Hodgkin lymphoma.



Adapted from (25)

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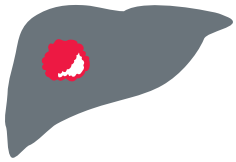
set the stage for the new era of precision medicine, an era in which the standard of care for many patients is changing from a one-size-fits-all approach to one in which greater understanding of the patient and his or her tumor dictates the best treatment option for the patient.

Therapeutics directed to the molecules involved in different aspects of the cancer process target the cells within a tumor more precisely than cytotoxic chemotherapeutics, 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 countless patients with cancer, but also allowing these individuals to have a higher quality of life than many who came before them.

In the 12 months spanning August 1, 2016, to July 31, 2017, the FDA approved seven new molecularly targeted anticancer therapeutics (see **Table 1**, p. 10). During this period, they also approved new uses for four previously approved molecularly targeted anticancer therapeutics, dabrafenib (Tafinlar), ibrutinib (Imbruvica), regorafenib (Stivarga), and trametinib (Mekinist).

Ibrutinib targets a protein called BTK, which is a component of a signaling pathway that promotes the survival and expansion of immune cells called B cells. In January 2017, the FDA granted accelerated approval to ibrutinib for treating certain patients with a type of non-Hodgkin lymphoma called marginal zone lymphoma, which arises in a certain population of B cells (see sidebar on **Accelerated Approval**, p. 63). The approval was based on results from a phase II clinical trial showing that ibrutinib caused significant tumor shrinkage in about 50 percent of patients whose disease had progressed despite standard-of-care treatment (129). This followed approvals in 2013, 2014, and 2015 for chronic lymphocytic leukemia and two other forms of non-Hodgkin lymphoma—mantle cell lymphoma and Waldenström macroglobulinemia—all of which also arise in B cells. These prior approvals were highlighted in earlier editions of the *AACR Cancer Progress Report* (1, 25).

Regorafenib targets proteins that promote the growth of new blood and lymphatic vessels, which tumors need to grow and survive. In April 2017, the FDA expanded the use of regorafenib to include the treatment of certain patients with the most common form of liver cancer, hepatocellular carcinoma, after it was shown in a phase III clinical trial to improve survival for patients with hepatocellular carcinoma that had progressed despite standard-of-care treatment with sorafenib (Nexavar) compared with placebo (130). The new approval followed approvals in 2012 and 2013 for colorectal cancer and gastrointestinal stromal tumors, which were highlighted in the *AACR Cancer Progress Report 2013* (33).



Regorafenib (Stivarga) is the **first** new anticancer therapeutic approved for treating advanced hepatocellular carcinoma **in a decade**.

The following discussion focuses on the other FDA approvals for molecularly targeted anticancer therapeutics that occurred in the 12 months covered by this report.

Adding Precision to Treatment for Acute Myeloid Leukemia

Acute myeloid leukemia (AML) is the most common type of leukemia diagnosed in the United States, with more than 21,000 new cases anticipated in 2017 (2). It is also the type of leukemia with the lowest overall five-year relative survival rate, 27 percent (5).

Treatment has changed little in the past few decades (131). It usually occurs in two phases. The first, which is known as the induction phase, includes an intensive course of cytotoxic chemotherapy designed to put the leukemia into remission. The second phase is known as the consolidation phase. It includes further cytotoxic chemotherapy or a stem cell transplant and it is designed to keep the leukemia in remission.

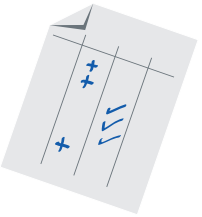
In recent years, research has substantially increased our understanding of the biology of AML, in particular the genetic mutations that fuel leukemia growth (132). One of the genes most frequently mutated in AML is FLT3, and patients with this form of AML have particularly poor outcomes (133).

This knowledge ultimately led to the first new FDA-approved treatment for AML in almost three decades, midostaurin (Rydapt). Midostaurin is also the first molecularly targeted therapeutic approved for treating AML. It targets several related molecules called tyrosine kinase receptors, including FLT3 and KIT, and it was approved by the FDA in April 2017 for treating adults newly diagnosed with AML harboring a mutation in the FLT3

Companion Diagnostics

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

are stringently tested for accuracy, sensitivity, and fidelity;



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

accurately match patients with the most appropriate therapy;

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

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

Adapted from (1)

gene, as detected by an FDA-approved test, or companion diagnostic (see sidebar on **Companion Diagnostics**). At the same time, the FDA approved a companion diagnostic, the LeukoStrat CDx FLT3 Mutation Assay, to identify patients with AML with the FLT3 mutation.

Midostaurin was approved for use in both the induction and consolidation phases of treatment for AML after it was shown in a phase III clinical trial that patients with FLT3-mutated AML who received midostaurin and standard induction and consolidation cytotoxic chemotherapy had a more than 20 percent improvement in overall survival compared with those patients who received placebo with standard treatment (134).

In April 2017, the FDA also approved midostaurin for treating adults with certain aggressive forms of a rare disorder known as systemic mastocytosis. In patients with this disorder, immune cells called mast cells accumulate in internal organs such as the liver, spleen, bone marrow, and small intestines.

Research has shown that most cases of systemic mastocytosis are caused by mutations in the gene that encodes the KIT tyrosine kinase receptor, which is one of the targets of midostaurin (135). The approval of midostaurin for treating aggressive systemic mastocytosis, systemic mastocytosis with associated hematological neoplasm, and mast cell leukemia was based on clinical trial results showing that a proportion of patients with these disorders benefited from the molecularly targeted therapeutic (136).

Targeting Soft Tissue Sarcoma

Soft tissue sarcomas are a diverse group of more than 70 types of cancers that arise in soft tissues of the body, such as the muscles, tendons, fat, blood vessels, lymph vessels, nerves, and tissues around joints. These cancers are rare; 12,390 U.S. adults are expected to be diagnosed with a soft tissue sarcoma in 2017 (2).

Patients with metastatic soft tissue sarcoma have a poor prognosis. Many are treated with the cytotoxic chemotherapeutic doxorubicin, either alone or in combination with other cytotoxic chemotherapeutics, but even then overall survival is estimated to be just 12 to 16 months (137).

In October 2016, the FDA made a decision that provides a new treatment option for patients with advanced soft tissue sarcoma. Specifically, the agency granted accelerated approval to the molecularly targeted therapeutic olaratumab (Lartruvo) for treating patients with soft tissue sarcoma who cannot be cured with radiation or surgery

and who have any type of soft tissue sarcoma that would normally be treated with a cytotoxic chemotherapeutic such as doxorubicin (see **Figure 12**). The FDA accelerated approval program was initiated to expedite the assessment of therapeutics for life-threatening diseases such as cancer (see sidebar on **Accelerated Approval**). A requirement of such approvals is that additional clinical testing must be undertaken to confirm that the therapeutic does indeed provide clinical benefit for patients as anticipated. If the outcome of a clinical trial is not as anticipated, the FDA will review the decision and could remove the therapeutic from the market.

Olaratumab is a monoclonal antibody that targets the protein platelet-derived growth factor receptor-alpha (PDGFRA). The rationale for testing it as a potential treatment for soft tissue sarcoma came from numerous lines of research, including a study showing that targeting PDGFRA had antitumor activity in animal models of certain sarcomas (139).

Consistent with this rationale, a phase II clinical trial that included patients with more than 25 subtypes of metastatic soft tissue sarcomas showed that adding olaratumab to doxorubicin treatment nearly doubled median overall survival extending it by almost a year (140). This is very good news for patients like **Evan Freiberg** (see p. 66). Given that the FDA decision for olaratumab was an accelerated

Accelerated Approval

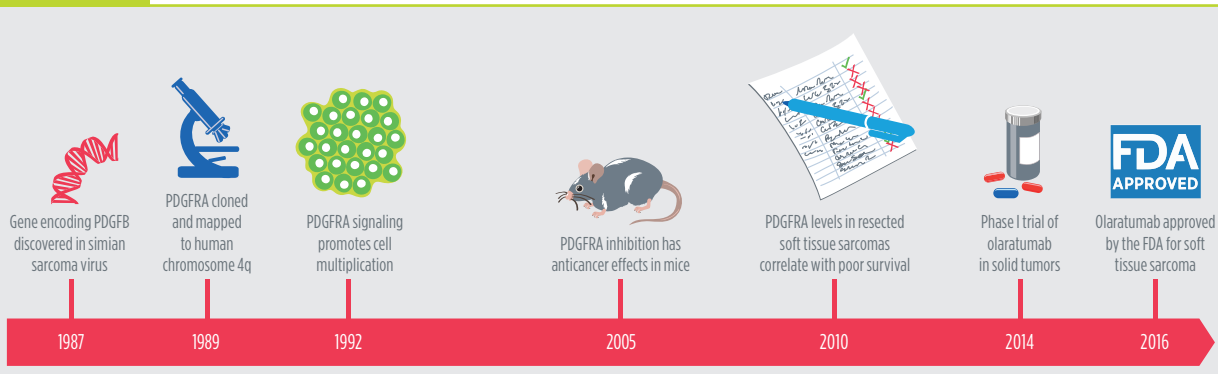
The accelerated approval program is one of four evidence-based strategies used by the U.S. Food and Drug Administration (FDA) to expedite the assessment of therapeutics for life-threatening diseases such as cancer.

Accelerated approval is based on assessing the effect of a therapeutic at an earlier stage than usual by using a surrogate endpoint. A surrogate endpoint is a marker, such as a radiographic image showing tumor shrinkage, that is thought to predict clinical benefit, which is defined as prolongation of survival or improved quality of life. The surrogate endpoint is not itself a measure of clinical benefit.

Any therapeutic approved through this program must undergo additional clinical testing to verify that it does provide the anticipated clinical benefit. If the confirmatory trial shows that the therapeutic does provide clinical benefit, then the FDA grants traditional approval. If the confirmatory trial does not show that the therapeutic provides clinical benefit, the FDA has the option of removing the therapeutic from the market.

Figure 12

The Pathway to Progress against Soft Tissue Sarcoma



Olaratumab (Lartruvo) is an anticancer therapeutic that targets the protein platelet-derived growth factor receptor-alpha (PDGFRA). Its October 2016 U.S. Food and Drug Administration (FDA) approval was the culmination of almost three decades of basic, translational, and clinical research. The story began in 1987, when researchers discovered a gene they called PDGFB. Through basic research, it was determined that this protein can attach to the protein PDGFRA, triggering a signaling pathway that promotes cell multiplication. Olaratumab prevents proteins such as PDGFB from attaching to PDGFRA and thereby prevents cell multiplication.

Data from (138)

approval, confirmation of the benefit of the molecularly targeted therapeutic is being evaluated in a phase III clinical trial.

Increasing Options for Patients with Ovarian Cancer

Ovarian cancer is the fifth most common cause of cancer-related death among U.S. women (2). In 2017 alone, it is expected that 14,080 women will die from the disease. One reason that ovarian cancer poses such a large challenge is that 60 percent of patients are first diagnosed when the cancer is already at an advanced stage.

Platinum-based cytotoxic chemotherapeutics are part of treatment for most women with advanced ovarian cancer. However, the majority of ovarian cancers that initially respond to this treatment eventually recur and are said to have become treatment resistant (141). In some patients, a second round of chemotherapy that includes additional or higher doses of platinum-based cytotoxic chemotherapeutics can be beneficial.

In March 2017, the FDA approved the molecularly targeted therapeutic niraparib (Zejula) for use in helping to address the challenge of resistance to platinum-based cytotoxic chemotherapeutics. Specifically, the agency approved niraparib for the maintenance treatment of patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancers that are responding to platinum-based cytotoxic chemotherapeutics. The approval was based on results from a phase III clinical trial showing that niraparib significantly extended the time to disease progression for women whose ovarian cancer had recurred after initial treatment but still remained responsive to platinum-based cytotoxic chemotherapeutics (142). Although the benefit was seen when considering all the women in the trial together, the improvement in progression-free survival was greater among patients who had inherited mutations in either the BRCA1 or BRCA2 genes than among those who had not inherited mutations in these genes. This approval is providing hope for patients with ovarian cancer, like **Teri Woodhull** (see p. 70).

The reason that the presence or absence of BRCA1 or BRCA2 mutations is relevant relates to the way that niraparib works. Niraparib blocks the function of poly ADP-ribose polymerase (PARP) proteins. Basic research has 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 (see **Figure 13**, p. 65).

Before the niraparib approval, in December 2016, the FDA granted accelerated approval to another PARP inhibitor, rucaparib (Rubraca) (see sidebar on **Accelerated Approval**, p. 63). This approval was for treating women who have advanced ovarian cancer that harbors cancer-associated BRCA1 and BRCA2 gene mutations and that has progressed despite treatment with two or more cytotoxic chemotherapy regimens. At the same time, the FDA approved a new companion diagnostic, the FoundationFocus CDxBRCA test, to detect cancer-associated BRCA1 and BRCA2 gene mutations in ovarian cancer tissue samples and thereby identify those patients eligible for rucaparib treatment.

The approvals of rucaparib and FoundationFocus CDxBRCA were based on clinical trial results showing that rucaparib treatment led to tumor shrinkage in about 50 percent of patients with recurrent, advanced ovarian cancer with a cancer-associated BRCA1 or BRCA2 gene mutation (144, 145). The proportion of patients who benefited from rucaparib was greatest among those whose tumors were still responsive to platinum-based cytotoxic chemotherapeutics.

Three

PARP inhibitors have been approved by the FDA for treating certain patients with ovarian cancer: niraparib (Zejula), olaparib (Lynparza), and rucaparib (Rubraca).

Keeping Breast Cancer Cells at Bay

Despite major advances in the treatment of breast cancer, the disease is the second-leading cause of cancer-related death for women in the United States (2).

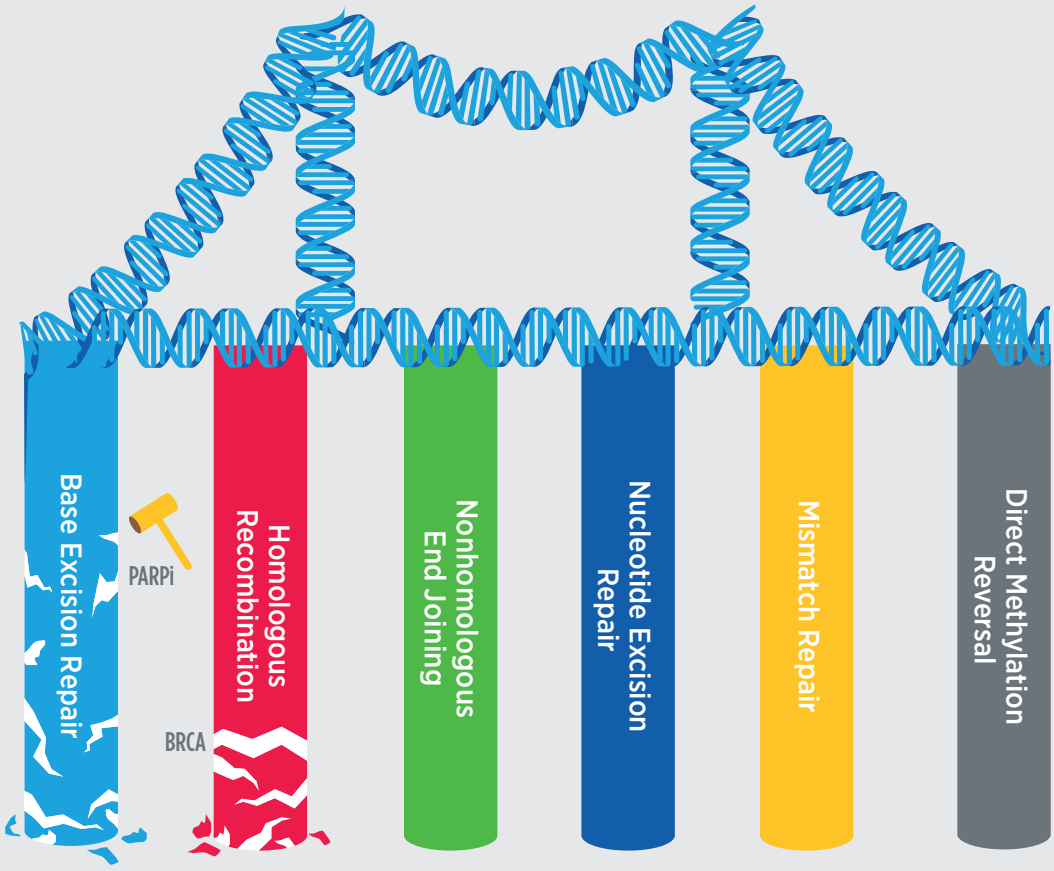
Most breast cancers are characterized by the presence of proteins called hormone receptors. The growth of these breast cancers is fueled by hormones, which attach in a lock-and-key fashion to the hormone receptors on individual breast cancer cells, stimulating the cells to multiply

and survive. This knowledge led to the development of therapeutics such as tamoxifen, which is an antiestrogen that works by preventing the hormone estrogen from attaching to its receptor, and letrozole, which is an aromatase inhibitor that works by lowering the level of estrogen in the body. These therapeutics have been used successfully for decades to treat patients with hormone receptor–positive breast cancer.

continued on **p. 68**

Figure 13

DNA Integrity: Bridging the Precision Gap



Basic research has shown that maintenance of DNA integrity is essential for a cell to remain healthy and maintain normal function. The integrity of DNA is constantly under threat from errors that occur during multiplication, as well as exposure to chemicals, such as those in cigarette smoke, and ultraviolet radiation from the sun. If DNA is not appropriately repaired, mutations accumulate, increasing the chance that a cell will become cancerous. As a result, cells have several interrelated pathways that they use to repair damaged DNA (143). The BRCA proteins are members of the homologous recombination DNA repair pathway (red support), and individuals with mutations in these proteins (BRCA label) have an increased risk of developing certain types of cancer. The PARP proteins are central to the base excision repair pathway (light blue support). Researchers have found that ovarian cancers with defective BRCA1 or BRCA2 genes are responsive to PARP inhibitors such as niraparib (Zejula) and rucaparib (Rubraca) because they lead to such pervasive DNA damage that the cancer cells die.

Figure adapted from (25)

EVAN FREIBERG, MD, PHD
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HOPING TO LIVE A NORMAL LIFE

THANKS TO SURGERY, RADIOTHERAPY, AND OLARATUMAB

In October 2016, I learned that my leiomyosarcoma, which had originally been confined to my left ankle, had spread to my lungs. Since then I've had surgery, radiotherapy, and received doxorubicin and olaratumab (Lartruvo). My hope is that this combination approach to treatment will allow me to live a normal life. I want to grow old with my wife and see my young children graduate high school and get married.

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> " My hope is that this **combination approach** to treatment will **allow me to live a normal life**. "

At the start of November 2015, I was finally able to relax after a stressful six months during which my second child was born, we moved, I started a new job, and I took and passed my diagnostic radiology board certification exams. I've always been an active person, so I joined a gym and started running again.

That was when the intermittent pain I had been experiencing in my left ankle for about a year began to get worse. I put it down to the running and the fact that I was getting older; I was 41. X-rays ordered 6 months earlier by a podiatrist had shown nothing unusual but after the pain worsened I had an MRI. It showed a 5-centimeter mass in my left ankle. A biopsy revealed that the mass was leiomyosarcoma, a rare type of cancer arising in smooth muscle cells.

My reaction to the diagnosis would probably surprise most people. I wasn't shocked; I just wanted a plan to deal with it. Through my job as a radiologist who specializes in breast imaging, I've diagnosed hundreds of women with breast cancer, so I've seen that cancer can strike anyone at any time. Not many people expect cancer but it happens, and now it had happened to me.

The first part of my plan was to find a specialist. The orthopedic oncologist I saw at Memorial Sloan Kettering Cancer Center recommended that I have a below the knee amputation of my left leg. Before I went ahead with such a life-changing surgery, however, I obtained a second opinion and had a second biopsy, this time an open surgery biopsy.

Once the diagnosis was confirmed, I was at peace with the decision to amputate. The surgery was February 2, 2016.

I was back in the gym shortly after the surgery, even before I had my prosthetic leg fitted in March 2016. Exercise really helps me. When I exercise, I don't feel like a cancer patient; I feel in charge of my body and that is very important to my mental well-being. Completing a sprint triathlon just seven months and one day after the amputation was a huge achievement for me, especially as just a month later, in October 2016, a follow-up surveillance CT scan showed a growing nodule in my right lung, the most common site for leiomyosarcoma metastases.

During minimally invasive surgery on the right lung, the surgeon removed eight nodules, seven of which turned out to be metastatic disease. So, I started eight cycles of the chemotherapeutic doxorubicin and a newly FDA-approved drug called olaratumab. We know this has stabilized my disease because the nodules in my left lung and the nodule in my hip have stayed the same size and no new nodules have appeared.

We are hoping that the doxorubicin and olaratumab have also killed any remaining leiomyosarcoma cells that are not visible on scans. To be sure, I'll be continuing with olaratumab for at least six months longer. Because we are going for a cure, I've also just completed six radiotherapy treatments to eliminate the nodule in my hip and I'm scheduled for open surgery to remove the nodules in my left lung at the end of July 2017.

My hope is that the cancer will not come back and that I will have a normal life expectancy for an otherwise healthy 43-year-old. I want to keep enjoying life and doing all the normal things that a family does.

I also hope that if the cancer does come back, the research currently being done will have resulted in a clinical tool that can help me. Before I was a radiologist, I was a research chemist, so I know how long it takes before basic research can change lives. The platelet-derived growth factor receptor [PDGFR], which is the target of olaratumab, first had to be discovered through basic research before olaratumab could be developed. This is why funding for basic research is so important; it give patients hope of a longer survival. ■

continued from **p. 65**

Unfortunately, most advanced, hormone receptor–positive breast cancers that initially respond to antiestrogens and aromatase inhibitors eventually progress because they have become treatment resistant. A recent FDA decision is helping to address this challenge by providing a way to prolong the time before a cancer becomes resistant to treatment.

In March 2017, the FDA approved the molecularly targeted therapeutic ribociclib (Kisqali) for use in combination with an aromatase inhibitor for treating postmenopausal women with hormone receptor–positive, HER2–negative, advanced breast cancer.

Ribociclib works by blocking the function of two specific proteins that play a role in driving cell multiplication—cyclin-dependent kinase (CDK) 4 and CDK6 (see **Figure 14**). Its FDA approval was based on results from a phase III clinical trial that showed that adding ribociclib to the aromatase inhibitor letrozole significantly increased the time to disease progression among postmenopausal women newly diagnosed with advanced, hormone receptor–positive, HER2–negative breast cancer (146). Longer follow-up of these patients has recently shown that the combination also improves overall survival (147).

Research has shown that other breast cancers are characterized by the presence of elevated levels of the protein HER2 and that signaling networks triggered by HER2 stimulate the breast cancer cells to multiply and survive. HER2-positive breast cancers tend to be aggressive; the outcome for patients was typically very poor until researchers harnessed the basic understanding of the biology of these cancers to develop a number of therapeutics that target HER2. Trastuzumab (Herceptin) was the first of these molecularly targeted therapeutics to be approved by the FDA in 1998.

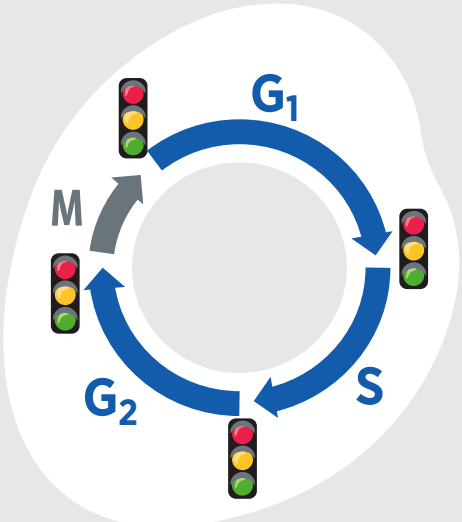
One use for trastuzumab in the treatment of patients with HER2-positive breast cancer is as an adjuvant treatment for those with early-stage disease, meaning it is given after

Five

HER2-targeted therapeutics have been approved by the FDA for treating certain patients with breast cancer: ado-trastuzumab emtansine (T-DM1; Kadcyla), lapatinib (Tykerb), neratinib (Nerlynx), pertuzumab (Perjeta), and trastuzumab (Herceptin).

Figure 14

Checking Cell Multiplication



Cell multiplication is a cyclical process with numerous checkpoints (traffic lights) at which it can be stopped, temporarily or more permanently. The phases of the cycle between the checkpoints have different names (G1, S, G2, and M). Cyclin-dependent kinase (CDK) 4 and CDK6 are two proteins that promote passage through the checkpoint between the G1 and S phases of the cell cycle. Blocking these proteins can prevent cell multiplication. There are two anticancer therapeutics approved by the FDA that exert anticancer effects by targeting CDK4 and CDK6, palbociclib (Ibrance) and ribociclib (Kisqali). They were approved for treating certain patients with breast cancer in February 2015 and March 2017, respectively.

Figure adapted from (25)

the patient has completed his or her initial treatment to lower the risk that the cancer will recur. In this setting, trastuzumab is usually given for one year after surgery and chemotherapy.

Even though one-year adjuvant trastuzumab significantly improved outcomes for patients with early-stage HER2-positive breast cancer, more than 20 percent of patients still have disease recurrence (148, 149). A recent FDA decision is helping to address this challenge by providing a way to reduce the risk of recurrence.

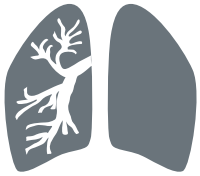
In July 2017, the FDA approved the HER2-targeted therapeutic neratinib (Nerlynx) for use as an extended adjuvant treatment for patients with early-stage HER2-positive breast cancer who have completed one year of adjuvant treatment with trastuzumab. The approval was based on results from a phase III clinical trial that showed after two years of follow-up, women with early-stage HER2-positive breast cancer who received 12 months of neratinib after one year of trastuzumab were significantly less likely to have invasive disease recurrence compared with those who received placebo (150). Given that diarrhea was a common adverse event among those who received neratinib, the FDA recommends that patients receiving the newly approved HER2-targeted therapeutic should be given antidiarrheal prophylaxis for the first 56 days of treatment and as needed thereafter.

Helping Some Lung Cancer Patients Breathe Easier

Recent advances against lung cancer are grounded in research discoveries, including the identification of several genetic changes that fuel cancer growth in certain patients and the development of therapeutics that target these changes.

The most recent of these advances occurred in June 2017, when the FDA approved the use of a combination of molecularly targeted therapeutics, dabrafenib (Tafinlar) and trametinib (Mekinist), for the treatment of non–small cell lung cancer (NSCLC) harboring a specific mutation in the BRAF gene called BRAF V600E.

This approval was built upon prior research focused on melanoma (151). The discovery that 50 percent of melanomas are fueled by the abnormal BRAF V600E protein generated as a result of the BRAF V600E mutation had led to the development of several BRAF V600E–targeted therapeutics, including dabrafenib, and several therapeutics, including trametinib, that block the activity of two other proteins, MEK1 and MEK2, that function in the same signaling network as BRAF V600E. The combination of dabrafenib and trametinib was approved by the FDA for treating melanoma with BRAF mutations, including BRAF V600E mutations, in January 2014.



Lung cancer is the leading cause of cancer-related death in the United States (2).

More recently, we have learned that the BRAF V600E protein fuels the growth of 1 to 2 percent of NSCLCs (152). The dabrafenib and trametinib combination was approved to treat patients with metastatic NSCLC fueled by the BRAF V600E protein after it was shown to cause complete or partial tumor shrinkage in about 60 percent of patients (152).

At the same time as approving dabrafenib and trametinib for treating NSCLC, the FDA approved a companion diagnostic to identify patients eligible for the combination treatment (see sidebar on **Companion Diagnostics**, p. 62). The Oncomine Dx Target Test is the first companion diagnostic to use next-generation sequencing technology, which means it can provide information on not just one gene but on multiple genes. In fact, it provides information on 23 genes, including BRAF, EGFR, and ROS1. There are FDA-approved molecularly targeted therapeutics for treating NSCLC harboring EGFR and ROS1 mutations, gefitinib (Iressa) and crizotinib (Xalkori), respectively. Thus, the FDA has approved the Oncomine Dx Target Test for identifying patients with NSCLC eligible for treatment with crizotinib, gefitinib, and the dabrafenib and trametinib combination.

Unfortunately, most lung cancers that initially respond to molecularly targeted therapeutics eventually progress because they have become treatment resistant.

In April 2017, the FDA granted accelerated approval to a molecularly targeted therapeutic called brigatinib (Alunbrig), providing a new option to help patients with NSCLC harboring mutations in the ALK gene address the challenge of treatment resistance.

Research has shown that ALK gene mutations fuel 3 to 7 percent of cases of NSCLC, which is the most commonly diagnosed form of lung cancer in the United States (2). This has led to the development of a number of anticancer therapeutics targeting ALK. Crizotinib was the first of these to be approved by the FDA, in August 2011, and it is now the standard of care for patients with metastatic ALK-positive NSCLC. Unfortunately, not all patients with NSCLC driven by ALK have tumor shrinkage after crizotinib treatment. Moreover, the majority of patients whose cancer initially

■ ■ ■ *continued on* ***p. 72***

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Age 54
Minnetonka, Minnesota

KEEPING OVARIAN CANCER AT BAY

THANKS TO CLINICAL TRIALS

Since I was diagnosed with advanced ovarian cancer in November 2010, I have opted to be treated through clinical trials because they give me something beyond the standard of care. Most recently, I have been receiving a targeted therapy called niraparib (Zejula). Although this treatment is not a cure, it has kept the cancer at bay for more than 2 years. It is also giving me a quality of life that was not possible with chemotherapy.

© AACR/Todd Buchanan

told me that they were sure there was a hereditary aspect to the disease in my family.

I was fortunate to be living near the Mayo Clinic in Minnesota where they were investigating whether young women from families with a strong history of breast cancer, like me, would be prevented from developing breast cancer by having a bilateral mastectomy. I had the procedure in 1993, at the age of 30.

About a year later, the first breast cancer susceptibility gene, BRCA1, was identified. I was aware of this but chose not to be tested because I thought I had done everything I could to protect myself and there was no law at the time to protect people from genetic discrimination in health insurance and employment. Fortunately, now there is the Genetic Information Nondiscrimination Act.

What I didn't know was that BRCA gene mutations also increase risk for other cancers. It was only after my advanced ovarian cancer diagnosis that I was tested and found to have inherited a BRCA1 mutation.

I really didn't have many symptoms before my diagnosis apart from constipation. It wasn't until I could feel something in my abdomen that I went to the doctor. MRI and CT scans and a CA125 blood test showed that I had ovarian cancer that had spread beyond my abdominal cavity. I had advanced disease.

I was working in the health care field at the time and I knew that the survival statistics for women with my diagnosis were not good. After surgery, during which they removed all visible disease, I thought enrolling in a clinical trial would improve my chances of beating the statistics. The trial I participated in was testing whether giving chemotherapy directly into the abdomen, rather than into the blood, would reduce disease recurrence. It was also testing whether maintenance therapy with bevacizumab (Avastin) after the chemotherapy would help. Tolerating the chemotherapy was tough but I made it through and by the middle of 2011, just as I started the maintenance bevacizumab, there was no evidence of disease.

Unfortunately, a CT scan in the fall of 2014 showed that the cancer was back. I had surgery again and then standard chemotherapy. It was brutal. I was barely functioning; it was hard to get up, get dressed, eat, anything.

> " Every scan that shows **niraparib** is still **keeping the cancer stable** reminds me how fortunate I am. "

With chemotherapy, I could barely get out of bed. With niraparib, I've traveled the world with my family; I've been on safari in South Africa and hang gliding over the Swiss Alps.

Cancer has been part of my life for almost as long as I can remember. My mom died of breast cancer in 1990, at the age of 46. Her mother had breast cancer and my mother's cousin had breast cancer in her 40s. In 1990, even before there were any known breast cancer susceptibility genes, the doctors

Even worse, when I met the gynecological oncologist to get the results of the routine CT scan after finishing the chemotherapy, I learned that the cancer had progressed. It was a sobering moment, but I'm a positive person, and I was determined to keep living.

After a lot of research, I managed to get a spot on a clinical trial testing the targeted therapy niraparib. It was in San Francisco, so I've had to travel back and forth a lot over the past 2½ years. The day I started the trial, I took the red eye home and then flew the next day to my daughter's graduation. It was pretty crazy. But cancer has taught me that my family and friends are the most important things in my life and I take every opportunity to spend time with them and be there for the important life events.

At this point, I have CT scans every 12 weeks. Every scan that shows niraparib is still keeping the cancer stable reminds me how fortunate I am. I also know that the path I chose, participating in clinical trials, is helping make a difference to the future of ovarian cancer care. ■

continued from p. 69

responds to the ALK-targeted therapeutic eventually relapse because the cancer becomes resistant to the agent.

In many cases, crizotinib resistance emerges because NSCLC cells acquire additional ALK mutations. Research has shown that brigatinib is able to block many of the unique forms of ALK that result from these new mutations (153). It was approved after phase II clinical trial results showed that brigatinib treatment caused complete or partial tumor shrinkage in about 50 percent of patients with advanced, crizotinib-resistant NSCLC driven by ALK (154). Brigatinib was also able to shrink tumors that had metastasized to the brain in more than 40 percent of patients who had measurable brain metastases, which is something that not all ALK-targeted therapeutics are able to do so effectively.

Brigatinib is the fourth ALK-targeted therapeutic to be approved for treating patients with metastatic NSCLC fueled by ALK mutations. Two, crizotinib and ceritinib (Zykadia), are approved for use as the initial treatment for patients newly diagnosed with this disease. The other two, brigatinib and alectinib (Alecensa), are approved only for treating patients whose cancer has either progressed after treatment with crizotinib or has failed to respond to crizotinib in the first place. Identifying the order in which the four FDA-approved ALK-targeted therapeutics should be used to provide the maximum benefit for patients is an area of intensive research investigation. Initial results from one large phase III clinical trial recently showed that alectinib treatment significantly lengthened the time before disease progressed among patients newly diagnosed with metastatic NSCLC fueled by ALK mutations compared with crizotinib treatment (155). Whether this holds true for patient survival and how it affects long-term outcomes following sequential use of the four FDA-approved ALK-targeted therapeutics requires further research.

Treatment with Immunotherapeutics

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 flu and the bacterium that causes strep throat. Not all immunotherapeutics work in the same way (see sidebar on **How Immunotherapeutics Work**, p. 73).

The use of immunotherapeutics in the treatment of cancer is referred to as cancer immunotherapy. In recent years, it has emerged as one of the most exciting new approaches to cancer treatment that has entered the clinic. This is in part because some of the patients with metastatic disease who have been treated with these revolutionary anticancer treatments have had remarkable and durable responses, raising the possibility that they might be cured. It is also because some of the immunotherapeutics have been shown to work against an increasingly broad array of cancer types (see **Figure 15**, p. 74).

Despite the significant advances that have been made, only a minority of patients who are treated with an FDA-approved immunotherapeutic have a remarkable and durable response. In addition, the current FDA-approved immunotherapeutics are not highly active against all types of cancer. Identifying ways to increase the number of patients for whom treatment with an immunotherapeutic yields a remarkable and durable response is an area of intensive basic and clinical research investigation.

Several approaches are already being tested in clinical trials for a wide array of cancer types, including evaluating how well immunotherapeutics that are already FDA approved work in combination and how well they work in combination with investigational immunotherapeutics that function in novel ways, such as by directly boosting the killing power of cancer-fighting immune cells. Also being tested are various ways to combine FDA-approved immunotherapeutics with other types of anticancer treatments, including radiotherapy, cytotoxic chemotherapeutics, and molecularly targeted therapeutics (see **Improving Outcomes by Combining Existing Treatments**, p. 56).

As research deepens our scientific understanding of the immune system and how it interacts with cancer cells, we are likely to develop many new immunotherapeutics and identify novel ways to use those that we already have. One approach that is already showing incredible promise, in particular for children with acute lymphocytic leukemia, is referred to as CAR T-cell therapy (156, 157). Here, however, we focus on immunotherapeutics that were approved by the FDA in the 12 months covered by this report, August 1, 2016, to July 31, 2017.

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 them from attacking the cancer cells. These brakes, which are on the surface of T cells, are called immune-checkpoint proteins.

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

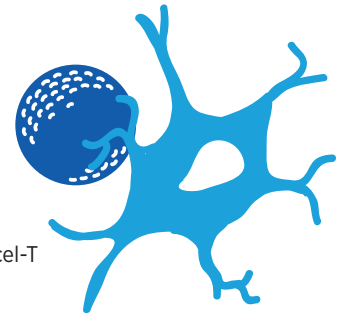
The first checkpoint inhibitor to be approved by the FDA was ipilimumab (Yervoy). It targets the immune-checkpoint protein CTLA4, protecting it from the proteins

How Immunotherapeutics Work

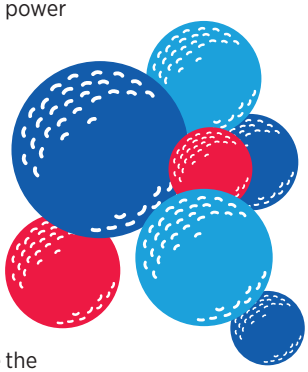
The way in which different immunotherapeutics unleash a patient's immune system to fight cancer varies:

Some release the brakes on the natural cancer-fighting power of the immune system, for example, avelumab (Bavencio) and durvalumab (Imfinzi) (see **Releasing the Brakes on the Immune System**, p. 72).

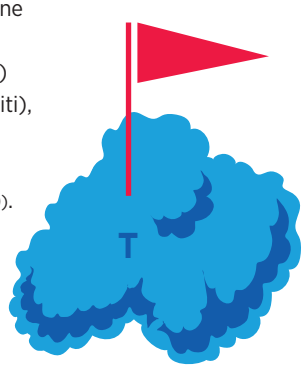
Some enhance the cancer-killing power of the immune system by triggering cancer-fighting T cells; these are called therapeutic cancer vaccines, for example, sipuleucel-T (Provenge).



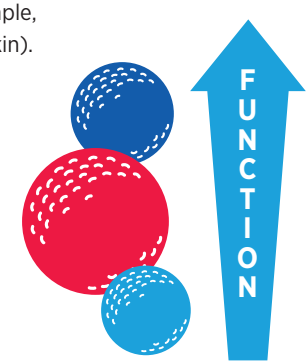
Some increase the killing power of the immune system by providing more cancer-targeted immune cells called T cells; these are called adoptive T-cell therapies, for example the CAR T-cell therapy CTL019. For more information on these immunotherapeutics see the *AACR Cancer Progress Report 2015* (25).



Some flag cancer cells for destruction by the immune system, for example, daratumumab (Darzalex) and elotuzumab (Empliciti), which were highlighted in the *AACR Cancer Progress Report 2016* (30).



Some boost 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), which was highlighted in the *AACR Cancer Progress Report 2016* (30).

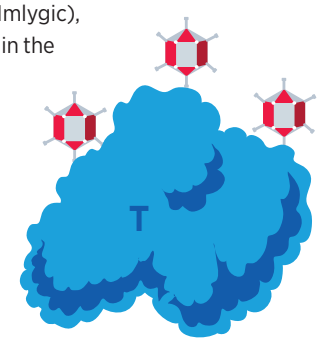


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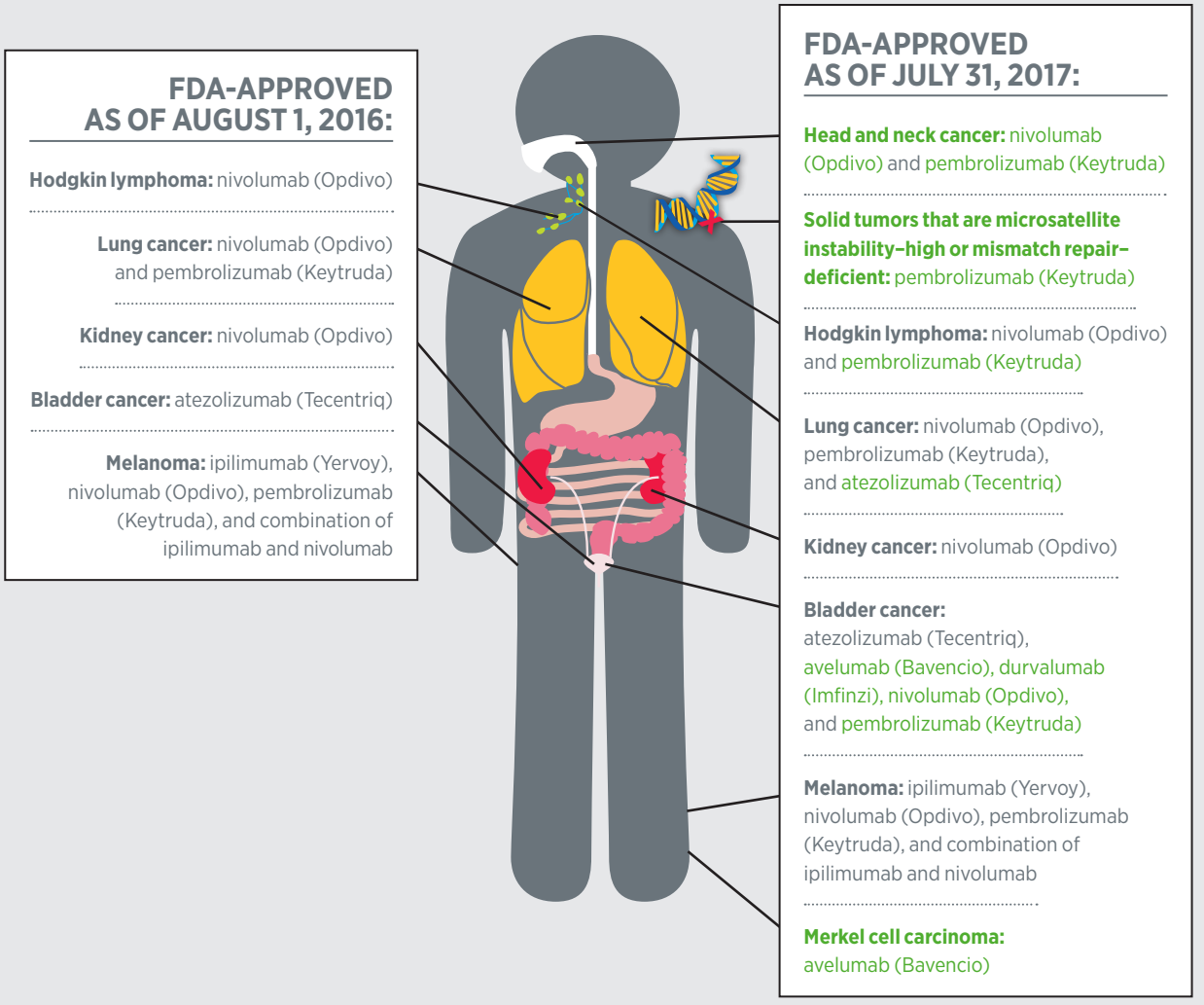
Figure 15

The Expanding Scope of Checkpoint Inhibitors



Cancer immunotherapeutics are anticancer therapeutics that work by unleashing the power of a patient's immune system to fight cancer the way it fights pathogens like the virus that causes flu and the bacterium that causes strep throat. One class of cancer immunotherapeutics works by releasing brakes on the surface of immune cells called T cells, which are naturally capable of destroying cancer cells. These revolutionary anticancer agents are called checkpoint inhibitors. In the 12 months covered by this report, August 1, 2016, to July 31, 2017, there was a dramatic increase in both the number of checkpoint inhibitors approved by the U.S. Food and Drug Administration (FDA) and the number of uses for which they are approved (shown in green). On August 1, 2016, there were four FDA-approved checkpoint inhibitors and there was one or more checkpoint inhibitor approved for treating five types of cancer. As of July 31, 2017, there were six FDA-approved checkpoint inhibitors and there was one or more checkpoint inhibitor approved for treating seven types of cancer and for treating any type of solid tumor characterized by the presence of specific molecular characteristics, or biomarkers.

Figure adapted from (30)

that attach to it and trigger it to put the brakes on T cells. The approval of ipilimumab for treating certain patients with metastatic melanoma in March 2011 followed almost 25 years of basic and clinical research (see **Figure 16**). In October 2015, the FDA expanded the approved uses of ipilimumab to include its use as adjuvant therapy for patients with stage 3 melanoma to reduce the risk of disease recurrence after surgery.

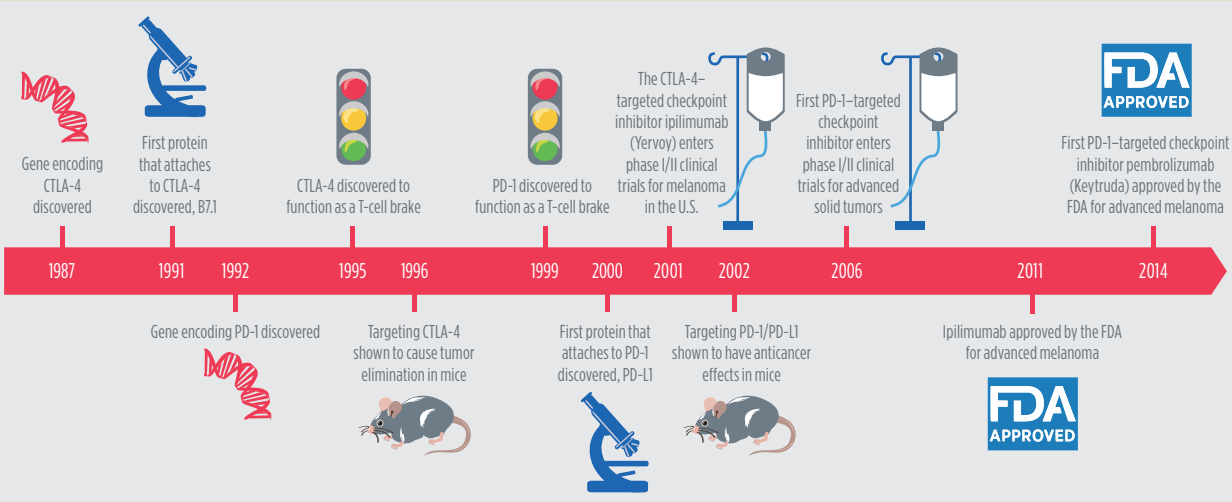
Motivated by the success of ipilimumab and the need to provide new treatment options for patients who did not respond long-term to ipilimumab, researchers focused on targeting a second checkpoint protein, PD-1, as well as one of the proteins that attaches to it, PD-L1. The first FDA approval of a checkpoint inhibitor targeting PD-1 or PD-L1 occurred in September 2014, when pembrolizumab (Keytruda), which targets PD-1, protecting it from being triggered, was approved for treating certain patients with metastatic melanoma (see **Figure 16**). By July 31, 2016, two other checkpoint inhibitors targeting PD-1 or PD-L1 had been approved by the FDA—atezolizumab (Tecentriq), which targets PD-L1, and nivolumab (Opdivo), which targets PD-1—and the three immunotherapeutics were approved for treating several types of cancer (see **Figure 15**, p. 74).

From August 1, 2016, to July 31, 2017, the number of checkpoint inhibitors that target PD-1 or PD-L1 approved by the FDA increased from three to five. In addition, the FDA substantially expanded the approved uses for each of the three previously approved PD-1/PD-L1–targeted checkpoint inhibitors to include additional types of cancer (see **Figure 15**, p. 74).

One of the expanded uses for PD-1/PD-L1–targeted checkpoint inhibitors was the May 2017 accelerated approval of pembrolizumab for treating certain adults and children with solid tumors characterized by the presence of specific molecular characteristics, or biomarkers, called microsatellite instability–high and DNA mismatch–

Figure 16

Stops along the Way to Developing Checkpoint Inhibitors



Checkpoint inhibitors are cancer immunotherapeutics that work by releasing brakes on the surface of cancer-fighting immune cells called T cells. The first checkpoint inhibitor to be approved by the U.S. Food and Drug Administration (FDA) was ipilimumab (Yervoy), in March 2001. It targets a brake on T cells called CTLA-4. Several other checkpoint inhibitors target a second T-cell brake called PD-1. The first of these immunotherapeutics to be approved by the FDA was pembrolizumab (Keytruda), in September 2014. More than 20 years of basic and clinical research underpinned the development of ipilimumab and pembrolizumab, starting with the discoveries of the CTLA-4 and PD-1 genes in 1987 and 1992, respectively (158, 159). Other basic research milestones along the way to the FDA approvals include the identification of the brake function of CTLA-4 and PD-1 (160–162), identification of the proteins that attach to and trigger the brake function of CTLA-4 and PD-1 (163, 164), and the demonstration that immunotherapeutics targeting these brakes can protect them from being triggered (165, 166).

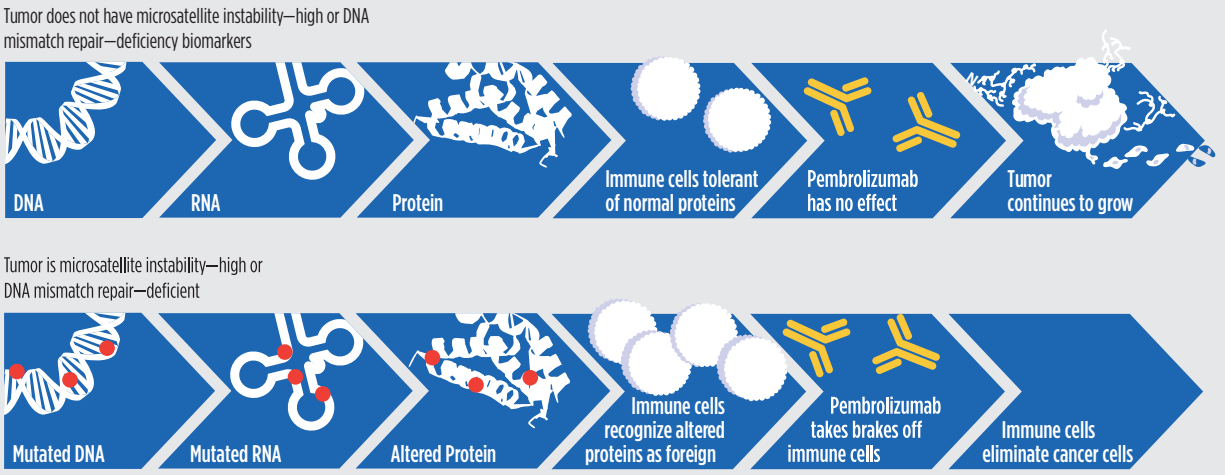
Figure adapted from (33)

repair deficiency. These biomarkers are found in a small proportion of cancers arising at numerous sites in the body, including the colon, endometrium, stomach, and rectum (167). As of July 31, 2017, this is the only FDA approval of an anticancer therapeutic based on a common biomarker and not the location in the body where the cancer originated. It is also an example of precision immunotherapy, whereby a patient's immunotherapy is tailored to the molecular characteristics of his or her tumor (see **Figure 17**).

The approval was based on data from several clinical trials showing that pembrolizumab treatment led to tumor shrinkage in about 40 percent of patients with an unresectable or metastatic, microsatellite instability–high or DNA mismatch–repair deficient solid tumor that had progressed despite prior treatment (169). The patients included in the analysis had been diagnosed with any one of 15 types of cancer, most commonly colorectal cancer. Their tumors had been shown to be microsatellite instability–high and DNA mismatch–repair deficient using specific molecular tests, such as those that are already in use for identifying patients with Lynch syndrome, a disorder caused by inherited mutations in DNA mismatch–repair genes that significantly increases a person's risk of developing certain types of cancer, including colorectal cancer and endometrial cancer (see **Table 3**, p. 22). Thus, the approval provides new treatment options and new hope to patients with a wide range of types of cancer, in particular for those with Lynch syndrome, like **Adrienne Skinner** (see p. 78).

Figure 17

More Precisely Identifying Tumors Likely to Respond to Checkpoint Inhibitors



Precision medicine is broadly defined as treating a patient based on characteristics that distinguish that patient from other patients with the same disease. The U.S. Food and Drug Administration (FDA) accelerated approval of pembrolizumab (Keytruda) for the treatment of any solid tumor identified to be microsatellite instability–high or DNA mismatch–repair deficient is an example of precision immunotherapy. The scientific rationale underpinning this approval was the result of dedicated researchers integrating scientific discoveries in the fields of immunology and cancer biology to develop an understanding of why microsatellite instability–high and DNA mismatch–repair deficiency are effective biomarkers for the use of pembrolizumab. Cancer cells with these biomarkers have many mutations in their DNA. These mutations give rise to altered proteins, which are recognized as abnormal, or foreign, to cancer-fighting immune cells called T cells. These T cells are spurred into action when the PD-1 brake that is preventing them from eliminating cancer cells is released by pembrolizumab. In cancer cells that are not microsatellite instability–high and DNA mismatch–repair deficient, there are dramatically fewer DNA mutations and, therefore, few altered proteins. The immune cells in this situation accept the protein landscape in the tumor as normal and are unlikely to be spurred into action by pembrolizumab. Motivated by the strong scientific rationale for using microsatellite instability–high and DNA mismatch–repair deficiency as biomarkers for pembrolizumab treatment, researchers are currently testing whether these biomarkers are also effective for identifying patients likely to benefit from treatment with other PD-1/PD-L1–targeted checkpoint inhibitors including nivolumab (Opdivo) (168).

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

The FDA also expanded the uses for PD-1/PD-L1–targeted checkpoint inhibitors to include the treatment of squamous cell carcinoma of the head and neck, which is the most common form of head and neck cancer, providing new hope for patients like **Bill McCone** (see p. 82). In late 2016, nivolumab and pembrolizumab were both approved by the FDA for treating patients with recurrent or metastatic squamous cell carcinoma of the head and neck that has progressed despite treatment with a platinum-containing chemotherapeutic. In the case of pembrolizumab, accelerated approval was granted based on the fact that treatment with the checkpoint inhibitor led to tumor shrinkage in up to 20 percent of patients (170). For nivolumab, full approval was granted based on results from a phase III clinical trial that showed that nivolumab improved survival compared with a cytotoxic chemotherapeutic, which is the standard of care for patients with recurrent or metastatic squamous cell carcinoma of the head and neck that has progressed despite treatment with a platinum-containing chemotherapeutic (171).

A new type of cancer for which checkpoint inhibitors became an FDA-approved treatment is a rare, aggressive form of skin cancer called Merkel cell carcinoma. In March 2017, one of the new checkpoint inhibitors, avelumab (Bavencio), which targets PD-L1, preventing it from attaching to PD-1 and triggering its brake function, was approved for treating patients with metastatic Merkel cell carcinoma. The accelerated approval was based on the fact that treatment with avelumab led to tumor shrinkage in about 30 percent of patients enrolled in a phase II clinical trial (172). With this decision, avelumab became the first treatment approved by the FDA for Merkel cell carcinoma, providing new hope to patients like **Carrie Best** (see p. 86).

Head and neck cancer is actually a group of cancers that includes cancers of the oral cavity, larynx, pharynx, salivary glands, and nose/nasal passages.

The second new checkpoint inhibitor to be approved by the FDA in the 12 months covered by this report is durvalumab (Imfinzi), which also targets PD-L1. It was granted accelerated approval for treating certain patients with the most common form of bladder cancer, urothelial carcinoma, in May 2017. Specifically, it was approved for treating patients with locally advanced or metastatic urothelial carcinoma whose disease has progressed despite treatment with a platinum-based cytotoxic chemotherapeutic. The decision was based on the fact that treatment with durvalumab led to tumor shrinkage in about 16 percent of patients enrolled in a phase II clinical trial.

Three of the other PD-1/PD-L1–targeted checkpoint inhibitors were also approved by the FDA for treating patients with locally advanced or metastatic urothelial carcinoma whose disease has progressed despite treatment with a platinum-based cytotoxic chemotherapeutic in 2017. The accelerated approvals for nivolumab and avelumab, which were made in February 2017 and May 2017, respectively, were based on phase II clinical trial results showing that treatment with the checkpoint inhibitors led to tumor shrinkage in up to 20 percent of patients (173, 174). The May 2017 full approval for pembrolizumab was based on results from a phase III clinical trial that showed that treatment with the checkpoint inhibitor improved survival compared with treatment with a cytotoxic chemotherapeutic, which is the standard of care for patients with locally advanced or metastatic urothelial carcinoma that has progressed despite treatment with a platinum-containing cytotoxic chemotherapeutic (175). The fifth PD-1/PD-L1–targeted checkpoint inhibitor, atezolizumab,

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Merkel cell carcinoma is a rare, aggressive type of cancer that affects

about 1,500

people in the United States each year.

ADRIENNE SKINNER
Age 60
Larchmont, New York

LIVING LIFE TO THE FULL

THANKS TO RESEARCH

I was diagnosed with metastatic ampullary cancer in February 2013. After 13 months of various chemotherapies, none of which kept the cancer at bay for more than a few months, my oncologist told me that my best hope for a good outcome was a clinical trial testing an immunotherapy called pembrolizumab (Keytruda). After 2½ months, the cancer was gone. I'm back to living my life as a busy working single mother of four daughters. I play tennis, I do yoga, and I'm enjoying

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planning my eldest daughter's wedding.

My journey with cancer really began 12 years ago, when one of my sisters, who was 46 at the time, was found to have Lynch syndrome. Because Lynch syndrome is an inherited condition many of our family members underwent genetic testing. It turns out that my mother passed on the genetic mutation that causes Lynch syndrome to me and my sister and that I have passed it on to three of my four daughters.

Lynch syndrome dramatically increases the risk of many types of cancer. So, once I knew I had the condition, I was proactive about my health. I had a full hysterectomy to prevent gynecological cancers, I had a colonoscopy annually to check for polyps and colorectal cancer, and I had an endoscopy every other year to check for signs of other digestive tract cancers.

In my mind, it was a matter of when, not if, I would develop cancer. So, when routine blood tests showed my liver enzymes were off the charts and scans revealed a tumor blocking the bile duct and the pancreatic duct, the pragmatist in me came to the fore.

I set about finding the best medical care possible. After interviewing three surgeons, I chose to have the procedure at Memorial Sloan Kettering Cancer Center in New York. Unfortunately, it was not possible for my surgeon to complete the planned procedure because during the operation he saw that the cancer had spread to my liver. I had stage IV disease.

At this point, chemotherapy was my only option. The first chemotherapy I received was brutal. It made me so sick that I couldn't even sip water and after two weeks my oncologist, Dr. Eileen O'Reilly, had to switch me to a different chemo regimen. After about five months of this, the cancer started growing again and we had to switch to another chemotherapy.

Less than six months later, Dr. O'Reilly told me we needed to look for alternative treatments because the chemotherapy had stopped working again and the chances that more chemotherapy would solve the problem were slim.

During the year I had been under Dr. O'Reilly's care, genetic testing of my cancer had shown that it was MSI high, so she recommended that I try and enroll in a clinical trial testing an immunotherapy in people like me who had cancer that was MSI high. The trial was being conducted at the Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins in Baltimore.

At first it seemed that I might not be eligible for the trial because my liver enzyme levels were fluctuating wildly. However, they agreed to enroll me and I received my first dose of pembrolizumab on April 15, 2014. An endoscopy at the end of July 2014 showed that the main tumor was gone. In fact, the doctor who performed the endoscopy said: "If somebody hadn't told me you had ampullary cancer I wouldn't have known because there is nothing there."

It was a miracle.

I continued to receive pembrolizumab through the trial for 2 years. Given that I have Lynch syndrome it seemed like a good insurance policy for me. It's been more than 15 months since my last treatment and I'm still cancer free.

I still have regular follow-up scans for the ampullary cancer and I still continue to have annual colonoscopies and endoscopies because of the Lynch syndrome. My philosophy is to not waste time worrying about these things; life is too precious. Ampullary cancer was supposed to be a death sentence, but I'm alive thanks to the treatment I received through the clinical trial. I'm forever grateful to everyone who made this possible—the doctors, researchers, pharmaceutical companies, and people who funded the trial and the underlying research. ■

" Ampullary cancer was supposed to be a death sentence, but **I'm alive thanks to the treatment I received through the clinical trial**. "

Urothelial carcinoma is the most common type of **bladder cancer**, which is expected to be the sixth most commonly diagnosed cancer in the United States in 2017 (2).

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was granted accelerated approval for treating both patients with locally advanced or metastatic urothelial carcinoma that has progressed despite treatment with a platinum-containing cytotoxic chemotherapeutic and those for whom a platinum-containing cytotoxic chemotherapeutic is not an option.

In addition, in March 2017, pembrolizumab was granted accelerated approval for treating patients with classical Hodgkin lymphoma that has not responded to treatment or that has relapsed after three or more different treatments. The approval was based on results from a phase II clinical trial showing that pembrolizumab treatment led to tumor shrinkage in the majority of patients (176).

The number of uses for which atezolizumab is an FDA-approved treatment option was also expanded during the 12 months covered by this report. In October 2016, it was approved by the FDA for treating patients with metastatic NSCLC that has progressed despite treatment with a platinum-based cytotoxic chemotherapeutic or an appropriate molecularly targeted therapeutic. The approval was based on results from a phase III clinical trial that showed that atezolizumab improved survival compared with the cytotoxic chemotherapeutic docetaxel, which is standard of care for patients with metastatic NSCLC that has progressed during or after initial chemotherapy (177).

The successes highlighted here have led to clinical trials in which PD-1/PD-L1–targeted checkpoint inhibitors are being tested as a potential treatment for numerous other types of cancer. Results are not available yet for most of these trials. However, initial data show that pembrolizumab may benefit some patients with gastric cancer and mesothelioma (178, 179) and that nivolumab may benefit some patients with liver cancer (180).

Despite the rapid expansion in the number of FDA-approved checkpoint inhibitors and the number of FDA-approved uses for these revolutionary immunotherapeutics, it is important to note that several of the approvals were granted through the FDA accelerated approval program (see sidebar on **Accelerated Approval**, p. 63). As such, additional clinical testing is ongoing to confirm that the checkpoint inhibitors do indeed provide clinical benefit for patients as anticipated.

Additional clinical trials and longer follow-up of patients in the initial clinical trials are vital for deepening our understanding of the benefits and potential harms of checkpoint inhibitors. They may also lead to the identification of biomarkers that identify the patients most likely to benefit from a given treatment. This is important because it could allow a patient unlikely to benefit from a particular checkpoint inhibitor to be spared the potential toxicity of the treatment and to immediately start an alternative treatment, saving patients precious time in their race to find an effective therapy.

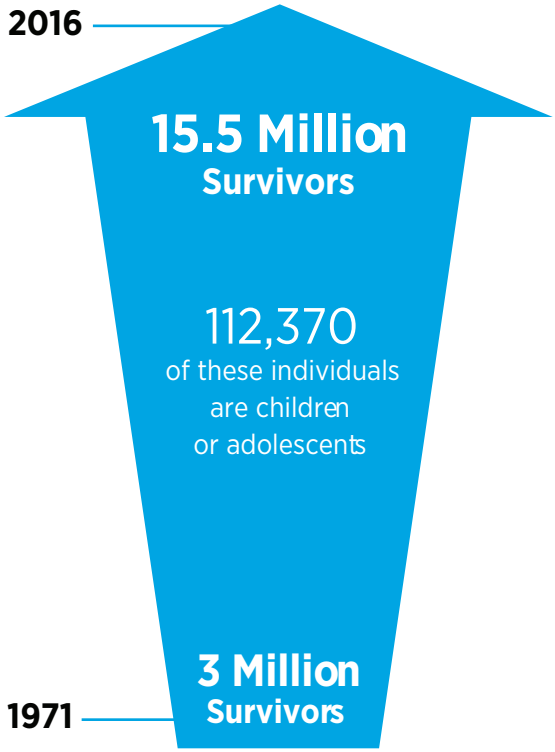
Currently, the only biomarkers used in the clinic for identifying which patients are most likely to benefit from a given PD-1/PD-L1 checkpoint inhibitor are the presence of PD-L1 in a tumor and the presence of microsatellite instability–high or DNA mismatch–repair deficiency in a solid tumor (see **Figure 17**, p. 76). These biomarkers are used for identifying those patients with lung cancer and those with solid tumors, respectively, who are most likely to benefit from pembrolizumab. In some other cases—for example, the use of durvalumab as a treatment for bladder cancer and the use of nivolumab as a treatment for lung cancer—the presence of high tumor levels of PD-L1 has been linked to a greater chance of benefit from a PD-1/PD-L1 checkpoint inhibitor. However, some patients whose tumors lack PD-L1 also benefited from these treatments. Thus, it is clear that new biomarkers are needed for identifying patients most likely to benefit from treatment with a checkpoint inhibitor, and this is an area of intensive research investigation (181).

Supporting Cancer Patients and Survivors

Research is driving advances in cancer detection, diagnosis, and treatment that are helping more and more people to survive longer and lead fuller lives after a cancer diagnosis. According to the latest estimates, more than 15.5 million U.S. adults and children with a history of cancer were alive on January 1, 2016, compared with just 3 million in 1971, and this number is projected to rise to 20.3 million by January 1, 2026 (182, 183).

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

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



long-term survival. Each phase of cancer survivorship is accompanied by a unique set of challenges (see sidebar on **Life after a Cancer Diagnosis in the United States**, p. 84). Recent advances in cancer treatment were discussed in the previous three sections of the report (see **Treatment with Surgery, Radiotherapy, and Cytotoxic Chemotherapy**, p. 56, **Treatment with Molecularly Targeted Therapeutics**, p. 57, and **Treatment with Immunotherapeutics**, p. 72). Several of the advances highlighted in these sections are helping to reduce the short-term adverse effects of treatment as well as the long-term and late effects of treatment. Here, the discussion focuses primarily on other recent advances that can help improve outcomes and quality of life for individuals in each distinct phase of cancer survivorship.

Importantly, the issues facing each survivor vary depending on many factors, including gender, age at diagnosis, type of cancer diagnosed, general health at diagnosis, and type of treatment received. Survivors of cancer diagnosed during childhood or adolescence (ages 0–19) are particularly at risk for critical health-related problems because their bodies were still developing at the time of treatment. In addition, those diagnosed with cancer as adolescents (ages 15–19) and young adults (ages 20–39) have to adapt to long-term cancer survivorship while beginning careers and thinking about starting families of their own.

More than
380,000
survivors of cancer diagnosed during childhood and adolescence are alive in the United States (184).

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

Optimizing Quality of Life across the Continuum of Cancer Care

One approach that can be used across the continuum of cancer care to optimize the quality of life for patients and their families is palliative care (see sidebar on **What Is Palliative Care?**, p. 85). Palliative care can be given throughout a patient's experience with cancer, beginning at diagnosis and continuing through treatment, follow-up, survivorship, and end-of-life care. The goal is not to treat the patient's cancer but to provide an extra layer of care that prevents or treats the symptoms and adverse effects of the disease and its treatment, as well as addresses the psychological, social, and spiritual challenges that accompany a cancer diagnosis.

Palliating Physical Symptoms

As research drives advances in cancer detection, diagnosis, and treatment, more and more people are living longer after a cancer diagnosis than ever before. As a result, palliating the physical symptoms and adverse effects of cancer and its treatment is becoming increasingly important.

In February 2017, the FDA approved a new treatment for palliating diarrhea in patients with carcinoid syndrome, telotristat ethyl (Xermelo). Carcinoid syndrome is a combination of symptoms that occur when a rare type of cancer called a carcinoid tumor secretes serotonin and other substances into the bloodstream. The symptoms include flushing of the face, diarrhea, and sudden drops in blood pressure. Treatment often includes therapeutics called somatostatin analogs, which work by blocking the release of serotonin and the other substances that cause carcinoid syndrome. However, these therapeutics do not control symptoms of carcinoid syndrome for all patients and even in those for whom they do work initially, symptoms usually return eventually. Telotristat ethyl works in a different way from somatostatin analogs to reduce the production of serotonin and has been shown in clinical trials to significantly reduce the frequency of bowel movements for patients with carcinoid syndrome when given in combination with a somatostatin analog (185).

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BILL MCCONE
Age 54
Gilbertsville, Pennsylvania

SURVIVING HEAD AND NECK CANCER

THANKS TO PEMBROLIZUMAB

In September 2014, I was told that my head and neck cancer had spread to my lungs and that with standard treatment I had about a year to live. I was also offered the opportunity to enroll in a clinical trial testing a drug called pembrolizumab (Keytruda). I took the opportunity, and after just 24 weeks, there was no evidence of cancer in my body. I was floored, but I'm living life to the full, camping, walking, and traveling with my wife.

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My journey with cancer began about a week before Thanksgiving in 2013. I tipped my head back to shave one morning and noticed I had a small lump in my neck. I kept feeling it for several days so my wife told me to go and get it checked out.

My family doctor sent me to an ear, nose, and throat (ENT) specialist at the local hospital who ordered a CT scan and a biopsy. The tests showed that the lump was a lymph node in my neck that was enlarged because of squamous cell carcinoma, although they didn't show the source of the cancer.

I was devastated. It felt as though my world had stopped and that everything else was just going on around me.

At that point, I wanted a second opinion at a specialized cancer center, so I went to Fox Chase Cancer Center in Philadelphia.

There they found that the primary cancer was in my left tonsil. Tests on a biopsy showed that the cancer was caused by HPV [human papillomavirus]. It was a total shock to me. I knew that my two daughters had received the HPV vaccine growing up, but my son had not. Right away, we got him vaccinated. I know that not everyone is having their children vaccinated, but I would strongly recommend vaccination over what I went through. I wouldn't wish my experience on anyone.

" **It is miraculous** what it **[pembrolizumab]** did ... "

My initial treatment was a six-week course of radiation. I also received weekly infusions of cetuximab (Erbitux). The cetuximab made me break out in itchy pimples, but the side effects of the radiotherapy were far worse. It caused blisters in my mouth and after about four treatments I couldn't eat anything. I lost 25 pounds in weight, dropping below 170 pounds, and I needed to drink seven Boosts a day for three-and-a-half months to maintain enough weight so as not to need a feeding tube. It was grueling.

My first CT scan after the initial treatment was in June 2014. They told me there was a 6-millimeter spot in one of my lungs but that I shouldn't worry about it because it could be anything. Three months later, the next CT scan showed that the spot had doubled in size and other spots were now visible.

The cancer had metastasized to my lung.

That was when the doctor told me that if I continued with standard treatment I had about a year to live. My wife and I looked at each other and our heads drooped. But a few minutes later, the doctor started talking about clinical trials. She told us that one of them was an immunotherapy trial and there were just two spots left. After thinking about it for a day, I enrolled.

My first infusion of pembrolizumab was in October 2014. I received it every three weeks for two years; I've been off it since September 2016. The only issue I've had was I developed hypothyroidism, but I take thyroid medication and it causes me no problems.

I had my first scan after starting pembrolizumab just before Christmas of 2014. It showed that the tumors had shrunk by 90 percent. I was amazed. Two scans later, there was no evidence of disease. Every scan since, including my last one in May 2017, has shown the same thing.

Hopefully, things stay this way and I can live my life. My wife and I have been going through a book called, *1000 Places to See Before You Die*, which she gave me before my diagnosis. We've been on an Alaskan cruise, and visited Yellowstone National Park, the Calgary Stampede, and Nashville. We can't wait for our next trip.

Maintaining funding for research is very important to me. The initial treatment I was on did not help me, but a new immunotherapy did. It is miraculous what it did, so let's keep the funding going and get this thing knocked out of the way. ■

Life after a Cancer Diagnosis in the United States

When an individual becomes a cancer survivor, his or her life is changed irrevocably. Cancer survivors often face serious and persistent adverse outcomes, including physical, emotional, psychosocial, and financial challenges as a result of the cancer diagnosis and treatment.

Among the challenges experienced from the time from diagnosis to the end of initial treatment are (182):

choosing a physician(s) and treatment facility;

choosing among a variety of treatment options; and

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

Many challenges experienced by cancer survivors begin during cancer treatment and continue long term, but others can appear months or even years later. These long-term and late effects include, but are not limited to (182):

bone density loss (osteoporosis);

cognitive impairment, sometimes known as "chemo brain";

diagnosis with a new form of cancer(s);

DISTRESS

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

FATIGUE

fatigue that is severe and often not relieved by rest;

FEAR

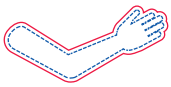
fear of cancer recurrence;

heart damage (cardiotoxicity);

INFERTILITY

infertility;

lung (pulmonary) damage;



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

pain;

premature aging;

recurrence of original cancer; and

SEXUAL DYSFUNCTION

sexual dysfunction.

Although all cancer survivors face challenges, survivors of cancer diagnosed from ages 0 to 19, during childhood and adolescence, are particularly at risk for severe long-term and late effects. The Children's Oncology Group's "Long-Term Follow-Up Guidelines for Survivors of Childhood, Adolescent, and Young Adult Cancers" were developed to help standardize and enhance the lifelong follow-up care of individuals who were diagnosed with cancer as children, adolescents, or young adults. For more information, see **http://survivorshipguidelines.org/.**

Adapted from (1)

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Given that uncontrolled diarrhea can be debilitating for patients, this approval provides a new option for improving their quality of life.

Hair loss is an adverse effect of treatment with many cytotoxic chemotherapeutics that has been reported to negatively affect quality of life, especially for women with breast cancer (186). In April 2017, the FDA cleared the use of a medical device to help palliate this quality of life issue for women with breast cancer. The device—the Paxman Scalp Cooling System—is worn by the patient while chemotherapy is administered. The cap cools the scalp, which is thought to reduce hair loss in two ways: First, by reducing blood flow to the scalp, which reduces the amount of chemotherapy that reaches cells in the hair follicles (hair roots) and second, by slowing down multiplication of cells in the hair follicles, which makes them less affected by chemotherapy. The cooling system was approved after it was shown in a clinical trial to be effective at reducing hair loss for women being treated with cytotoxic chemotherapeutics after a breast cancer diagnosis (187). In July 2017, the FDA expanded the number of cleared uses of a second cooling device, the Dignitana DigniCap Cooling System, from reducing hair loss for women with breast cancer being treated with cytotoxic chemotherapeutics to reducing hair loss for all patients with solid tumors being treated with cytotoxic chemotherapeutics.

Clearly, for a symptom to be treated, a health care provider has to know that the patient is experiencing the symptom. However, one study found that there is frequently no mention of a symptom in a patient's electronic medical record even if he or she has reported it on a patient-provided information form, suggesting that symptoms among patients with cancer are frequently undetected by the health care provider (188). The results from a recent study suggest that monitoring of electronic patient-reported symptoms might help address this issue (189). In this study, patients who provided self-reporting of 12 common symptoms at and between visits via a web-based patient-reported outcomes questionnaire platform had improved overall survival compared with those who had usual care. A report of a severe or worsening symptom triggered an email alert to a nurse who would respond, for example, by calling to provide symptom management counseling, providing supportive medications, modifying chemotherapy dose, or referring the patient for follow-up. Exactly how monitoring of the electronic patient-reported symptoms improved survival is not known, but it is possible that patients were able to tolerate chemotherapy longer as a result of symptom palliation.

This is just one example of the potential for patient-reported outcomes to enhance clinical care. Improved implementation of patient-reported outcomes into all phases of clinical care and into clinical trials is essential if we are to accelerate the pace at which we improve survival and quality of life for cancer patients and survivors.

What Is Palliative Care?

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

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

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

Palliative care addresses many of the challenges that can affect quality of life after a cancer diagnosis, including:

- emotional challenges such anxiety and depression;
- physical symptoms and adverse effects of the disease and its treatment, such as pain, nausea, vomiting, fatigue, difficulty sleeping, and loss of appetite;
- practical challenges such as navigating the health care system; and
- spiritual challenges.

Adapted from (30)

Psycho-oncology

A cancer diagnosis does not just pose physical challenges; it also poses behavioral, emotional, psychological, and social challenges. Researchers and health care practitioners working in the field of psycho-oncology are committed to developing new approaches to address these challenges, which include treatment-related cognitive impairment, fear of cancer recurrence, anxiety, depression, stress, and feelings of despair (see sidebar on **Helping Patients with Cancer through Psycho-oncology Research**, p. 88). 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, prolonged hospitalization during cancer treatment, and decreased survival (190–193).

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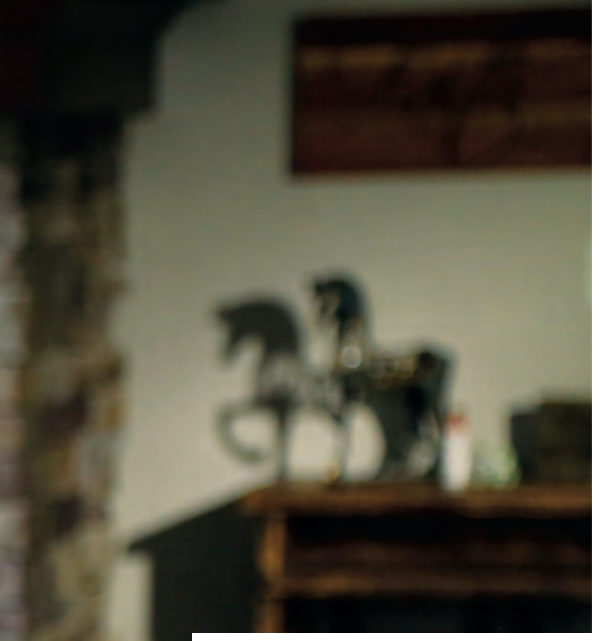
CARRIE BEST
Age 50
Plain City, Ohio

BEATING MERKEL CELL CARCINOMA

THANKS TO IMMUNOTHERAPY

In June 2014, I was told that I had about 8 weeks to live and that my only option was an immunotherapy clinical trial. Through this trial, I became the first person with Merkel cell carcinoma to receive avelumab (Bavencio). After just three treatments, the cancer was gone, and today I'm doing great. I'm working and enjoying the simple things in life with my husband and son, laying around in the hammock, riding our bikes, skiing, and generally having fun.



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carcinoma of unknown primary.

I took the call while sitting at a red light on my way to pick up my son from preschool. It took everything I had for me not to fall apart. After getting my son, I went to see my doctor, who is also a close friend, as his office was close by. The nurse took my son to another room, and then I broke down.

My friend had told me, "Carrie this is not good, this is a hardcore, mean cancer." So, when I saw the oncologist at The James who specialized in neuroendocrine carcinomas I already knew the seriousness of the situation. She told me that the lump in my armpit was a lymph node that was enlarged because the neuroendocrine carcinoma had spread there but she did not know where the original cancer was. She also told me that my chances of survival were less than 15 percent.

" After just three treatments, the cancer was gone, and today I'm doing great. "

I was diagnosed with cancer in May 2013, just days after my son had turned 6. I had woken up a few days earlier and felt a grape-sized lump in my armpit. Immediately I had thought of breast cancer—my mom had beaten breast cancer several decades earlier and because of that I had been in a breast cancer–surveillance program at The James†. But after several mammograms, ultrasounds, and a biopsy, the nurse practitioner called and told me it wasn't breast cancer, it was neuroendocrine

After seven cycles of platinum-based chemotherapy, I was cancer free. But just 3 to 4 months later, a scan showed cancer in a lymph node near my kidney. I was treated with everolimus (Afinitor) for 8 weeks, but the cancer spread through the lymph nodes in my pelvis. The chemotherapies I received through a clinical trial also failed to stop the cancer spreading. I knew the situation was dire.

Fortunately, the oncologist running the clinical trial I had been on did a molecular test on a sample of my cancer, and he told me he was 96 percent sure that the primary cancer was Merkel cell carcinoma.

Ever since my diagnosis, I had been educating myself about the latest in cancer research and clinical trials, but this was the piece of information I vitally needed to narrow down my online research. I had already been emailing and speaking to researchers around the world, but this diagnosis made me particularly interested in the idea of immunotherapy.

Just when I hit rock bottom, a response to one of my emails connected me to Dr. Howard Kaufman at the Cancer Institute of New Jersey in New Brunswick, who had just opened a clinical trial, testing avelumab as a treatment for Merkel cell carcinoma. Before I could enroll in the trial, they had to test my cancer to be 100 percent sure that it was Merkel cell carcinoma. I was overwhelmed when I found out all three molecular tests confirmed that it was.

I received my first infusion of avelumab in July 2014. After just three infusions, two weeks apart, I had my first scans. The nurse practitioner handed me the report as she prepared me for my fourth infusion. I had to read it over and over; it said that all my tumors had resolved. After what seemed like forever, Dr. Kaufman came over and confirmed what I had read; I was cancer free. It was one of the most powerful moments in my life.

There has been no sign of cancer since then, and in May 2015, Dr. Kaufman decided I do not need to take avelumab anymore.

Having stage IV cancer and coming so close to death has changed me, which has been hard for my friends and family. But in a lot of ways the changes are for the better. I spend every day thankful to be here. I am also grateful for the researchers who made this possible and I'm hopeful that the work they are doing will allow other people like me, mothers, fathers, sisters, brothers, husbands, wives, to have the same outcome that I have. ■

†The Ohio State University Comprehensive Cancer Center – Arthur G. James Cancer Hospital and Richard J. Solove Research Institute

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Modifying Behaviors to Improve Outcomes

Many factors related to lifestyle that increase a person's risk of developing cancer can also increase risk of cancer recurrence and reduce survival time (see **Figure 4**, p. 26). In some cases they have also been shown to increase a patient's risk of cancer treatment toxicity. Thus, modifying behaviors to eliminate or avoid these risk factors has the potential to improve outcomes and quality of life for cancer patients and survivors.

For example, research shows that quitting smoking can reduce risk of radiation-induced toxicity, risk of death from cancer, and risk for developing a second cancer (34). Even in the face of this knowledge, one study found that 9 percent of cancer survivors continue to smoke (200). Thus, more research is needed to develop optimal strategies to provide patients with cancer the best chance of quitting tobacco.

In addition, despite the knowledge that most cases of melanoma are attributable to UV light from the sun, sunlamps, tanning beds, and tanning booths (201), a recent study found that 19.5 percent of melanoma survivors report having had a sunburn in the previous year and 1.7 percent report having used a tanning booth or bed (202). Thus, it is clear that we need to develop more effective programs educating melanoma survivors, and indeed everyone, about the risks of UV exposure and to do more to address skin cancer as a serious public health challenge.

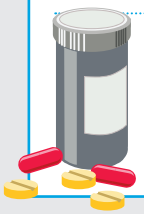
Evidence is also emerging that regular aerobic exercise can reduce recurrence and mortality in survivors of several types of cancer including early breast, prostate, and colorectal cancers (203). This evidence has largely come from observational studies, but it was recently shown in a small randomized exercise trial that patients with breast cancer who participated in supervised exercise, either aerobic or resistance, during chemotherapy tended to have improved disease-free and overall survival compared with those who did not have supervised exercise (204). The results of ongoing larger studies should provide more definitive answers about the role of exercise in improving cancer outcome (205).

Helping Patients with Cancer through Psycho-oncology Research

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

A **psychoeducational intervention** comprising a psychoeducational booklet and three individual telephone-based psychotherapeutic sessions with a psychologist effectively reduced stress and fear of cancer recurrence among survivors of melanoma (194).

A **psychosocial intervention** called Attention and Interpretation Modification for Fear of Breast Cancer Recurrence, which consisted of eight personalized treatment sessions, reduced health worries among survivors of breast cancer (195).



Treatment with the **psychedelic drug psilocybin** led to clinically significant reductions in depression and anxiety as well as improved quality of life (198, 199).

A **meaning-centered group psychotherapy intervention**, comprising eight group sessions led by a psychiatrist, clinical psychologist, or social worker, resulted in improved spiritual well-being and quality of life as well as reduced depression, hopelessness, desire for hastened death, and physical symptom distress among patients with advanced cancer (196).

A **web-based cognitive rehabilitation program** called Insight, which uses adaptive exercises to improve cognition through speed and accuracy of information processing, improved perceived cognitive function and quality of life and reduced depression, fatigue, and stress among adult cancer survivors who reported having chemo brain (197).

LOOKING TO THE FUTURE

In this section you will learn:

- The more we know about the biology of cancer and the individual in whom it occurs, the more precisely we are able to prevent, detect, diagnose, and treat cancer.
- "Big data" sharing initiatives will fuel a new era of cancer discoveries.
- Through research, some of the significant cancer health disparities that exists today can be eliminated tomorrow.

Moving toward Minimally Invasive Testing

Liquid biopsy refers to the collection and analysis of biofluids, such as blood or urine. In oncology it primarily involves the capture and analysis of cells, lipid-encapsulated sacs called exosomes, or free DNA shed by tumors into the blood. For example, a blood sample, rather than a biopsy of the tumor tissue itself, could be used to analyze genomic alterations in a patient's cancer. Currently, many liquid biopsy platforms are being developed and tested (206). The major advantages compared to traditional tissue biopsies are:

- Liquid biopsies have the potential to be safer, quicker, more convenient, and better representative of tumor heterogeneity than a typical biopsy.
- Liquid biopsies provide minimally invasive ways to repeatedly sample the genome of different tumor lesions to evaluate whether a cancer is responding to treatment or becoming treatment resistant and, if it is developing resistance, determine what treatment might be the most appropriate next option.

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

We have made some significant advances against cancer, with many more people living longer and fuller lives after a cancer diagnosis than ever before. Despite these advances, cancer continues to be an enormous public health challenge in the United States and worldwide (see sidebar on **Cancer: A Global Challenge**, p. 12). In fact, it is predicted that 600,920 people in the United States will die from some type of cancer in 2017 (2) (see **Table 2**, p. 13). However, many researchers, including the 2017–2018 AACR President, **Michael A. Caligiuri, MD**, are extremely hopeful about the future and are confident that through research we will power more advances against cancer (see p. 90).

FUELING A NEW ERA OF CANCER DISCOVERIES HARNESSING BIG DATA

As we move into the era of precision cancer medicine it is clear that a greater understanding of the molecular underpinnings of cancer will drive future progress in prevention, early detection, and treatment of the disease. Comprehensive molecular assessment of tumors will continue to uncover additional therapeutic targets that are altered in cancer. Minimally invasive tools such as liquid biopsies, which are being studied extensively, have the potential to advance early detection, diagnosis, and treatment by identifying markers of disease, therapeutic response, resistance, and recurrence (see sidebar on **Moving toward Minimally Invasive Testing**). However, to achieve the full potential of precision medicine, the molecular profile of a patient's cancer will need to be considered along with other factors, including the patient's genome, epigenome, microbiome, metabolome, lifestyle, and environmental exposures, which are emerging as important influences on cancer initiation, development, and progression.

To deepen our understanding of the many factors that influence cancer development and progression, we need to first generate and gather real world data, including patient history, diagnostics, genetic tests, treatment decisions,

continued on ***p. 92***

MICHAEL A. CALIGIURI, MD
AACR President, 2017–2018

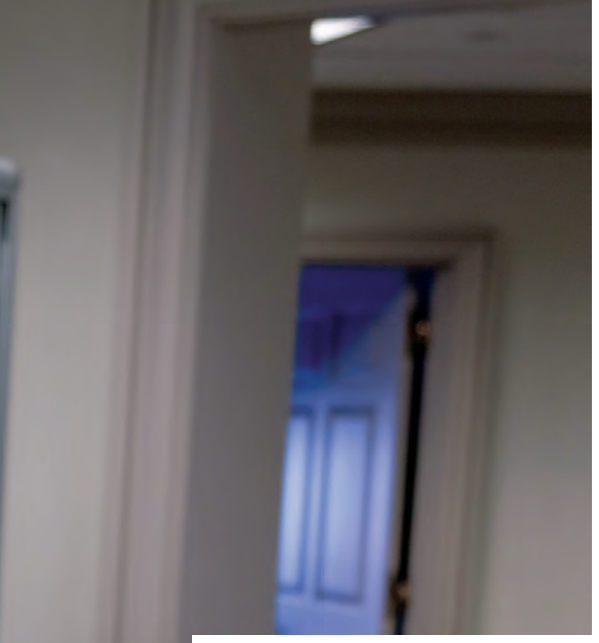
CEO, Arthur G. James Cancer Hospital and Richard J. Solove Research Institute, Columbus, Ohio

LOOKING FORWARD TO PROGRESS FOR ALL

FUELED BY BIG DATA

Since I was in medical school in the late 1970s, I have seen a transformation in cancer care. We have gone from having just a small number of drugs for treating most patients to being able to face the disease head-on with a range of therapies, not only surgery, radiotherapy, cytotoxic chemotherapy, but also molecularly targeted therapy and immunotherapy.

This change in cancer care is a result of tremendous advances in basic and applied research. Just as you need to



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collection, accumulation, and analysis of big data as holding the key to the next transformational breakthroughs. If you think about what a business such as Amazon does when you buy a book, that is what we hope big data initiatives like the American Association for Cancer Research (AACR) Project Genomics, Evidence, Neoplasia, Information, Exchange (GENIE) will do for the cancer field. After you select a single book to order on Amazon, you immediately see suggestions for other books you might be interested in, and the fact is you often would like to read those books. Amazon can do this because there are millions of people in its database. It finds thousands of people who have ordered the book you selected, analyzes the other books these people have ordered, and suggests the most common books to you.

> " As we move forward, I foresee the collection, accumulation, and analysis of **big data** as holding the key to the **next transformational breakthroughs.** "

In the next few years, as initiatives like AACR Project GENIE collect and accumulate data, we will be able to identify very small but uniform groups of patients that will provide researchers with opportunities to develop new treatments much more quickly than ever before. It may also allow patients and physicians to find patients like themselves and those they are treating, respectively, and learn what treatments these individuals have had.

In the longer term, as we learn more about how our DNA predisposes us to certain cancers or to tobacco addiction, we should be able to start to develop pharmacologic interventions that can help prevent cancer when used alongside behavioral interventions.

One of the challenges we face going forward is how to ensure that everyone benefits equally from the groundbreaking advances in cancer treatment and prevention that we are making. Cancer health disparities are already a huge problem. For example, African-Americans have the shortest survival for most cancers compared with those in other racial and ethnic groups in the United States. We need to do more to understand the reasons for disparities such as this and we need to address them. We know it is a complex, multifactorial problem that involves genetic, behavioral, and socioeconomic factors among others, and it will require a multifaceted, evidence-based approach to solving the problem.

Achieving our goal of creating a cancer-free world will require consistent, annual, above-inflation increases in the budget for the National Institutes of Health (NIH). Without this we will have less and less buying power, which will dampen the pace of progress. We will also lose some early-career investigators from the field. When I received my first R01 grant from the National Cancer Institute (NCI), the institute funded the top 20 percent of grant applications; in 2016 they funded around 10 percent. My first grants were rated in the 15th percentile, which means that in today's environment I would not have received funding and my contributions and the contributions of the 100 students that I have trained would have been erased.

We aren't asking for a doubling of the NIH budget or 50 percent of R01 grants to be funded, just real, above-inflationary growth and funding for one in every five R01 grant applications. This strategy will ensure that we move toward our goal of preventing and curing all cancers. ■

understand how an engine works to fix a car, you need to understand how a normal cell works and what happens when it becomes malignant to treat a cancer. That is what has happened in the last few decades. We have learned an enormous amount, at a very mechanistic level, about how normal cells behave, why they sometimes grow uncontrollably, and why they sometimes invade the surrounding tissues. This knowledge has led to advances in cancer treatment and prevention that are saving lives today.

As we move forward, I foresee the

continued from **p. 89**

and measured and patient-reported outcomes from large numbers of cancer patients. Using these data sets we could harness, and analyze patients' information to 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 cytotoxic chemotherapies. One way to accelerate the pace at which we gather patient-derived information is through data sharing across health care organizations throughout the United States and abroad. Approaches such as these will require cross-discipline collaboration among those working in basic, clinical, and translational sciences, biostatistics, epidemiology, mathematics, bioinformatics, and computational biology, among other disciplines. Extracting knowledge from large and complex data sets will also require unique processing applications, and concerted efforts from all sectors of the biomedical research community will be required to overcome the current technical as well as regulatory and ethical barriers to effective data sharing.

Several cancer organizations as well as multi-institutional teams have already launched a number of initiatives to catalyze data sharing (see **Table 6**, p. 93). A few examples of these cross-institutional projects are NCI Genomic Data Commons; BRCA Exchange (see sidebar on **Interpreting Genetic Tests**, p. 43); ASCO CancerLinQ; Oncology Research Information Exchange Network (ORIEN); and AACR Project Genomics, Evidence, Neoplasia, Information, Exchange (GENIE) (207). 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.

Charting the Future of Cancer Health Disparities Research

In 2015, representatives from four leading cancer organizations—the American Association for Cancer Research (AACR), the American Cancer Society (ACS), the American Society of Clinical Oncology (ASCO), and the National Cancer Institute (NCI)—began to meet to discuss the state of health disparities in the United States. The resulting position statement provides specific recommendations to improve the way disparities research is conducted and disseminated (208). The key recommendations aim to drive progress in five areas:

- Defining and improving measures and tools for cancer disparities research.
- Advancing knowledge of biologic and environmental determinants of cancer incidence disparities.
- Enhancing our understanding of the biologic, environmental, and system-level determinants of postdiagnosis survival to address cancer survival disparities.
- Advancing community engagement in cancer research and throughout the cancer care continuum.
- Redesigning clinical trials to acknowledge and address cancer disparities.

GREATER EFFORT TO REDUCE CANCER HEALTH DISPARITIES

Unquestionably, advances across the spectrum of research have spurred great progress in cancer prevention, detection, diagnosis, treatment, and, in some cases, cure. However, certain groups of individuals in the United States—in particular, racial and ethnic minorities and people of lower socioeconomic status—experience a notably higher incidence of some types of cancer and/or have significantly poorer outcomes (see **Disparities in Progress for Distinct Population Groups**, p. 11).

Through research, we have gained some knowledge about the factors that contribute to U.S. cancer health disparities (see sidebar on **Why Do Cancer Health Disparities Exist?** p. 17). However we have also learned that there are many of these factors and that they are interrelated, which makes them difficult to isolate and study individually.

To accelerate the pace of progress in this area, it is vital that all stakeholders, including researchers, cancer survivors, and health care providers, come together to ensure that research advances benefit all populations and patients regardless of race, ethnicity, age, gender identity, sexual orientation, socioeconomic status, or the communities in which they live. A recently published position statement from four leading cancer organizations—the AACR, the ACS, ASCO, and the NCI—provides specific recommendations for improving the way that disparities research is conducted and disseminated, and highlights one important effort to move the field forward (see sidebar on **Charting the Future of Cancer Health Disparities Research**) (208).

Table 6

Selected Cancer-focused Data Sharing Initiatives**

Name	Description	Intent	Access
100,000 Genomes Project	Genomics England-led whole genome sequencing initiative	Improve treatment and outcomes through personalized medicine	Authorized
American Association for Cancer Research (AACR) Project Genomics, Evidence, Neoplasia, Information, Exchange (GENIE)	International data-sharing project led by the AACR	Catalyze precision oncology by developing a regulatory-grade registry that aggregates, harmonizes, and links clinical-grade cancer genomic data with a select amount of clinical data for patients treated at multiple institutions and by making all de-identified data publicly available	Open
American Society of Clinical Oncology (ASCO) CancerLinQ	ASCO-led data acquisition and analysis system that collects clinical data from patients' electronic health records	Improve patient outcomes by tracking the quality of care in real time	Authorized
BRCA Exchange from The Global Alliance for Genomics and Health	A comprehensive, global data repository of BRCA1 and BRCA2 genetic variants and associated clinical data	Catalog all BRCA genetic variants and collect individual-level evidence for variants' pathogenicity	Open
Cancer Core Europe	A European consortium sharing a common translational genomic platform to conduct cutting-edge cancer clinical trials	Drive innovative translational research through data sharing	Authorized
Database of Genotypes and Phenotypes	National Center for Biotechnology Information-led repository of individual-level phenotype, exposure, genotype, and sequence data, and the associations between them	Allow complex analyses of genetic associations with phenotypic and disease characteristics	Open or authorized depending on study
Genomic Data Commons	A National Cancer Institute-led database to store, analyze, and distribute cancer genomics research data	Enable data sharing across cancer genomic studies in support of precision cancer medicine	Open or authorized depending on study
International Cancer Genome Consortium for Medicine (ICGCMed)	Links existing as well as new genomic data being generated, to clinical and health information, across the cancer spectrum	Develop preventive strategies, markers for early detection, more specific criteria and methods for diagnoses and prognoses, and interventions based on matching the molecular subtype of disease with the most effective combinations of therapies	Open or authorized depending on study
National Cancer Database	Clinical oncology database sourced from hospital registry data that are collected in more than 1,500 Commission on Cancer-accredited facilities; data represent more than 70 percent of newly diagnosed cancer cases nationwide	Analyze and track patients with malignant neoplastic diseases as well as their treatments and outcomes	Open
NCTN/NCORP Data Archive	Repository of patient-level data from phase III clinical trials that are part of National Clinical Trials Network (NCTN), Community Oncology Research Program (NCORP), and the Canadian Cancer Trials Group	Make data sets available in a timely manner and to researchers who wish to analyze the data in secondary studies to enhance the public health benefit of the original work	Authorized
Oncology Research Information Exchange Network (ORIEN)	Partnership among North American cancer centers coordinating collection and access to genomic, clinical, and epidemiologic data	Aid future clinical decision-making and advance precision cancer medicine	Authorized
Project Data Sphere	Repository of historical, patient-level, comparator-arm data from academic and industry phase III cancer clinical trials	Generate new insights into cancer research and enable new and innovative research	Authorized

** This list is not meant to be comprehensive

WORKING TOGETHER TO OVERCOME CANCER THROUGH PUBLIC POLICY

In this section you will learn:

- Increasing federal support for biomedical research and crosscutting research initiatives is crucial for progress against cancer.
- Regulatory science and policy play a key role in making continued progress against cancer.
- Federal support is needed to develop and train the biomedical research workforce of tomorrow.

CHAIRMAN
ROY BLUNT

AACR Annual Meeting, April 2, 2017

> "We must continue to firmly establish our federal commitment to the National Institutes of Health. We must remain focused on establishing a pattern of responsible investment through the appropriations process. We do not know the scientific advances that will be made in the next ten years, but we do know that if we keep investing in NIH, they will keep making lifesaving breakthroughs."

This is a time of incredible promise in cancer research. Scientific opportunities to spur advances against cancer that were previously unimaginable are now within reach. The progress is being made thanks to the efforts of countless researchers, physician-scientists, other health care professionals, and patient advocates working together across the continuum of biomedical research to unravel the complexity of cancer (see sidebar on **What Is Basic Research and How Does It Drive Progress against Cancer?** p. 19). This hard-won knowledge is leading to the development of new approaches for preventing, detecting, diagnosing, and treating cancer. More effective interventions improve patient quality of life and ultimately, save more lives from cancer.

As detailed in this report, the progress can be illustrated by the numbers. Between August 1, 2016, and July 31, 2017, the FDA approved nine new anticancer therapeutics and a new optical imaging agent to help visualize cancerous tissue during surgery. During this same period, the FDA also approved new uses for eight previously approved anticancer therapeutics.

The pace and scope of the advances are remarkable. Our knowledge of the complexities of cancer has been significantly enhanced, innovative new technologies have been developed, the number of uses for molecularly targeted therapeutics and immunotherapeutics has been dramatically expanded, and important progress has been made in cancer prevention and toward a better understanding of cancer health disparities.

The progress chronicled in this report would not be possible without strong, bipartisan leadership in Congress and federal support for the NIH, NCI, and FDA (see sidebar on **Building Blocks of Further Progress against Cancer**, p. 95). The AACR is deeply grateful to U.S. House and Senate leaders for making medical research a high national priority and establishing a new trend of significant, annual funding increases for the NIH and the NCI. For two consecutive years, robust funding increases have begun the process of reversing the troubling pattern of stagnant budgets that persisted for more than a decade and provided a much-needed investment at a critically important time. In addition, the NIH Innovation Fund, a multiyear, targeted funding stream created by the 21st Century Cures Act, will provide dedicated resources for the Beau Biden Cancer Moonshot to further accelerate progress in key areas where researchers are poised to make great strides.

ROBUST, SUSTAINED, AND PREDICTABLE FUNDING INCREASES FOR BIOMEDICAL RESEARCH

Federal funding through the NIH and NCI is the lifeblood of biomedical research and forms the foundation upon which most scientific and medical discoveries in the United States are made. In the years since President Nixon signed the National Cancer Act, investments in the NIH and NCI, in large part due to overwhelming bipartisan support from Congress, have resulted in the extraordinary progress against cancer detailed in this report.

continued on ***p. 98***

NCI-funded SWOG cancer treatment clinical trials have added about

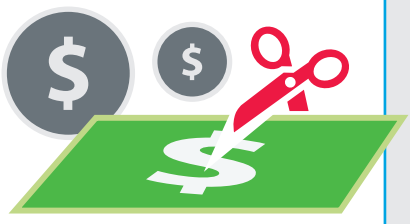
3.34 million years of life

for U.S. cancer patients at an estimated cost of just $125 for each year of life gained, according to a new study (209).

Turning Back the Clock

In his first budget proposal to Congress, President Trump proposed drastic and devastating cuts of $7.2 billion, or 20 percent, to the budget for the National Institutes of Health (NIH). This request would take funding for the agency back to levels not seen in more than 15 years and reduce the number of available grants by several thousand. If these cuts were enacted, a recent analysis predicted:

- Nearly 90,000 jobs nationwide would be lost.
- More than $15 billion in economic activity would be lost.
- No U.S. state would be spared from the negative impact of this dramatic reduction in federal funding, with 13,581 jobs predicted to be lost in California alone.



Building Blocks of Further Progress against Cancer

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

Prioritize and increase federal funding for biomedical research.

Support crosscutting initiatives to advance progress against cancer.

Support regulatory science initiatives.

Develop and train the biomedical research workforce of tomorrow.

Support policies that advance patient-centered research and care.

Adapted from (1)

THE HONORABLE CHARLIE DENT
U.S. Representative for Pennsylvania's 15th Congressional District
Age 57

WORKING RELENTLESSLY

TO ENSURE FUNDING FOR RESEARCH REMAINS A NATIONAL PRIORITY

Nearly everybody in the United States has been touched by cancer; either they have been diagnosed themselves or they have a family member or close friend who has been affected. Thanks to the work of scientists and physicians we have dramatically improved outcomes for patients with many types of cancer, but we can do better. That is why it is

© AACR/Karen Sayre

important for the federal government to invest in research.

I myself have had three very close family members who have had cancer. My mother was diagnosed with cancer back in the mid-1960s, when I was just three or four years old. I was too young to remember much, but her treatment at the University of Pennsylvania was successful, and we recently celebrated her 88th birthday.

My father-in-law and brother-in-law were not so fortunate. My father-in-law passed away from melanoma in January 2005, the day before I was sworn in to Congress for the first time. He had been diagnosed with metastatic melanoma just six months earlier, after having beaten it many years earlier. This experience deeply affected my family, and we are very careful to follow skin cancer prevention recommendations and be aware of sun exposure.

> " **The basic scientific and medical research** funded by the federal government through the monies it appropriates to the NIH, **drives discovery and the development of new therapies and even cures.** "

My brother-in-law passed away from colon cancer in February 2010. He was just 45 years old. My sister and their two young girls were devastated. This experience made me passionate about increasing awareness of and removing barriers to colorectal cancer screening, because we know that early detection improves outcomes. That is why the "Removing Barriers to Colorectal Cancer Screening Act of 2017," which I am sponsoring with Congressman Donald Payne, Jr. (D-NJ), is very important to me. If enacted, this new legislation would remove a barrier to colorectal cancer screening for Medicare beneficiaries. At present, Medicare will not pay the copay for the removal of a polyp(s) during a colorectal cancer screening colonoscopy. By eliminating this potential cost, we hope to increase the number of Medicare beneficiaries who undergo screening.

The experiences of my family members have also made me passionate about the work that I have done and continue to do as a member of the U.S. House of Representatives Committee on Appropriations. During the last session of Congress, when I served on the Labor, Health and Human Services, Education, and Related Agencies Subcommittee—which is the subcommittee that appropriates funds to the National Institutes of Health (NIH)—I am proud to say that we made funding medical research a high priority. We raised funding for the NIH by $2 billion in both fiscal year 2016 and fiscal year 2017.

These increases are critical because the NIH plays a vital role in improving the health and well-being of people worldwide. The basic scientific and medical research funded by the federal government through the monies it appropriates to the NIH, drives discovery and the development of new therapies and even cures. Federal investment in the NIH also improves the economic well-being of our nation and maintains America's leadership in the life sciences.

The work of the Appropriations Committee complements other legislative efforts that I have been involved with to expedite the development and approval of lifesaving therapies for people with cancer. I worked closely with Congressman Fred Upton (R-MI) on the 21st Century Cures Act, which provides a mechanism for supporting the Beau Biden Cancer Moonshot Initiative. This is such an exciting time; we have already made a lot of progress against cancer, and we as a country must do the right thing. I am committed to ensuring that the federal government will provide the money needed for us to do better. ■

continued from **p. 95**

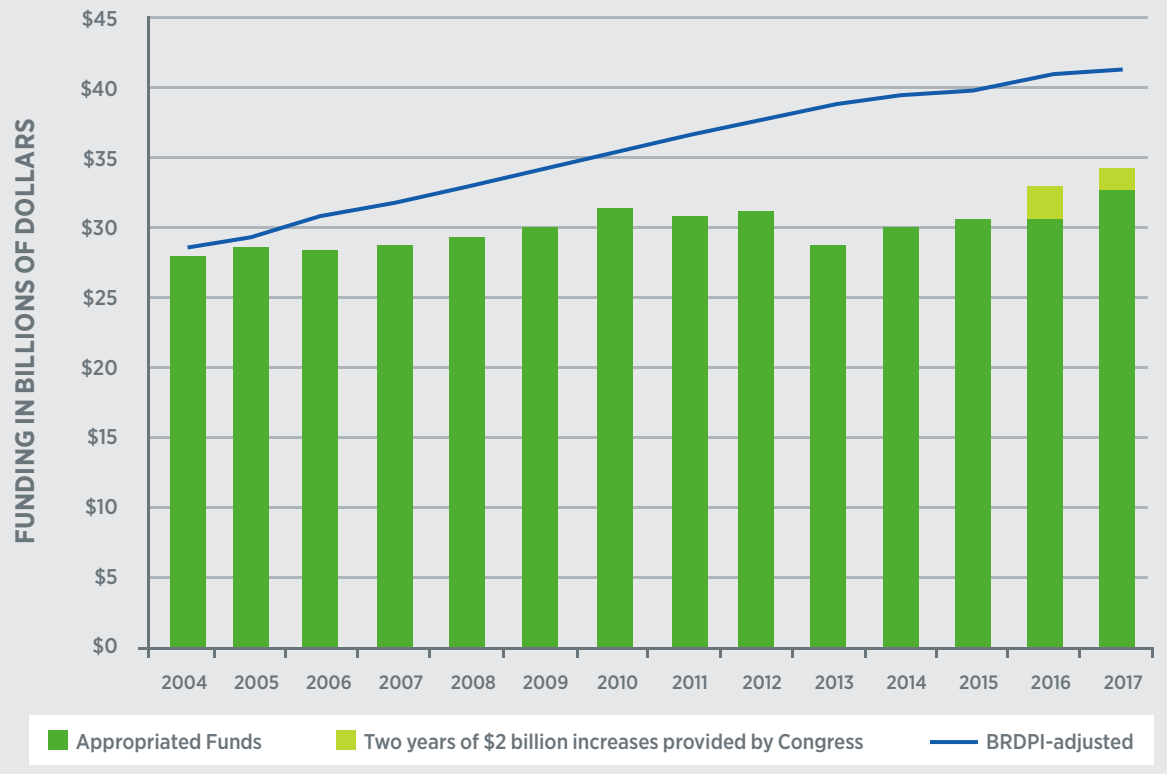
As discussed by **Congressman Charlie Dent**, strong federal investment in biomedical research is essential, both for our nation's health and for our economy (see p. 96). More than 80 percent of the funds appropriated by Congress to the NIH are distributed to scientists in all 50 states, the District of Columbia, and around the world to conduct research. In FY 2016, thanks to funding increases, the NIH supported 54,200 research grants, an additional 3,147 grants more than in FY 2014. The impact of federal support for NIH, NCI, and FDA reaches well beyond the laboratory and the clinic, supporting nearly $64.8 billion in economic activity last year alone.

Stagnant budgets at the NIH for more than a decade led to a 25 percent decline in its purchasing power, when adjusted for inflation. This factor, when combined with the growth in public funding of biomedical research by other countries, threatens the United States' position as the world leader in biomedical research. In the past two years through an extraordinary bipartisan effort, Congress halted this troubling downward trend with consecutive budget increases that outpaced inflation (see **Figure 18**).

However, the NIH now faces new threats to funding. In the spring of 2017, the Trump White House released a budget proposal that called for drastic cuts of more than 20 percent to the NIH in FY 2018 (see sidebar on **Turning Back the Clock**, p. 95). Unless a new budget agreement is reached between Congress and the White House, sequestration will return in FY 2018, in accordance with the Budget Control Act of 2011. It is imperative that Congress reject calls for cuts to this vital investment and instead, continue its commitment

Figure 18

Putting the NIH Budget Back on Track



The biomedical research and development price index (BRDPI) reflects the rising cost of personnel, supplies, and equipment needed to conduct biomedical research. From 2004 to 2015, the National Institutes of Health (NIH) budget did not keep pace with BRDPI. Thanks to Congressional leaders, the NIH received two consecutive years of significant funding increases in fiscal year (FY) 2016 and FY 2017, which have resulted in the first real budget growth in more than a decade. Continued support is required to close the gap created by years of budgets that failed to keep up with inflation and to ensure major progress against cancer and other diseases.

to robust, annual increases for the NIH so that funding can continue to recover lost ground and thereby yield results for all Americans and people around the world.

THE BEAU BIDEN CANCER MOONSHOT: TOWARD "ENDING CANCER AS WE KNOW IT."

The Beau Biden Cancer Moonshot is entering its second year, and in December 2016, the initiative received its first federal funding of $300 million through the NIH Innovation Fund, which was established in the 21st Century Cures Act (see sidebar on **Working Together to Implement the Beau Biden Cancer Moonshot**, p. 100). The initiative seeks to double the rate of progress toward a cure for cancer by making ten years of progress in five years.

Prior to leaving office, Vice President Biden delivered the Cancer Moonshot Task Force's comprehensive report to President Obama (210). In this report, Biden and his colleagues set forth a strategic plan for transforming cancer research and care through five overarching goals. The first goal, which is to catalyze scientific breakthroughs, will be accomplished through implementation of the recommendations of the Blue Ribbon Panel. The second goal is to unleash the power of data through several approaches, including the NCI Genomic Data Commons, which was unveiled in late 2016. This resource promotes the sharing of genomic and clinical data between researchers and serves to facilitate precision medicine in oncology. The third goal, to accelerate the delivery of new therapies to patients, is being accomplished in part through the creation of the FDA Oncology Center of Excellence (OCE) and the Partnership for Accelerating Cancer Therapies (PACT), which is a collaboration between the NIH and twelve biopharmaceutical companies, research foundations, and philanthropies.

The fourth and fifth goals are to strengthen the prevention and diagnosis of cancer, and to improve patient access and care, respectively. In conjunction with the release of the Cancer Moonshot Task Force report, Vice President Biden announced new commitments from both the public and private sectors to accomplish the goals set forth in the plan, including partnerships to advance data tools and patient services such as affordable and reliable transportation.

ENHANCING SUPPORT FOR REGULATORY SCIENCE AND POLICY ACTIVITIES AT THE FDA

The FDA is an integral part of the biomedical research cycle (see **Figure 8**, p. 49). Support of this critical agency through robust, annual appropriations from Congress is crucial if we are to continue to make advances against cancer through the delivery of safe, effective, and precise medical products to patients. This is because annual funding for the FDA from Congress goes toward the agency's regulatory science initiatives that seek to promote and develop new evidence-based regulatory policies that balance innovation and the expedited approval of medical products that are safe and effective.

As research leads to more sophisticated and complex approaches to treatment, the process of approving those therapies must keep pace. Likewise, the FDA must keep abreast of the latest scientific and technological progress through discourse, cooperation, and collaboration with academia, industry, patient advocacy groups, and government. In recent years, Congress has recognized that it must equip the agency with the resources it needs to support these regulatory processes. Thus, the 21st Century Cures Act included important provisions that provide a dedicated stream of funding to assist with innovation, expand hiring authority at the agency, and ensure continued professional development of staff.

The Aims of the FDA Oncology Center of Excellence

The FDA Oncology Center of Excellence (OCE) brings together regulatory scientists and reviewers with oncology expertise to support an integrated approach to driving progress against cancer. The goals of the OCE include:

- Ensuring that the patient perspective is considered in the regulatory decision-making process through a Patient-Focused Drug Development program.
- Encouraging novel clinical trial designs.
- Modernizing the eligibility criteria of cancer clinical trials by enrolling patients who reflect the real-world population, such as allowing more older adults to enroll.
- Striving for "excellence" within the OCE by collaborating externally with academia, industry, patient groups, and professional societies with the goal of expedited, risk-benefit ratio balanced drug development.

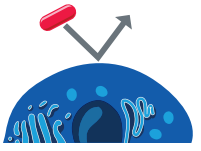
Working Together to Implement the Beau Biden Cancer Moonshot

At the White House on December 13, 2016, President Obama signed the 21st Century Cures Act into law. The legislation created an NIH Innovation Fund that provides $4.8 billion over 10 years in targeted, annual appropriations to three research initiatives, one of which is the Beau Biden Cancer Moonshot. Over seven fiscal years, beginning in fiscal year (FY) 2017, the Cancer Moonshot is to receive $1.8 billion through the NIH Innovation Fund. The first installment of $300 million was appropriated to the National Cancer Institute (NCI) in December 2016. The Beau Biden Cancer Moonshot is now under way thanks to the infusion of funding and the thoughtful recommendations set forth by the NCI Blue Ribbon Panel (BRP) in its September 2016 report (210). The BRP recommendations are:

- A network for direct patient engagement

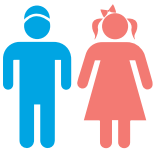
- A cancer immunotherapy clinical trials network

- Therapeutic target identification to overcome resistance



- A national cancer data ecosystem for sharing and analysis

- More research into fusion oncoproteins in pediatric cancer



- Symptom management research

- Implementation of evidence-based approaches in prevention and early detection

- A retrospective analysis of biospecimens from patients treated with standard of care

- Generation of human tumor atlases

- The development of new enabling cancer technologies

Implementation teams aligned with the BRP recommendations have been organized to both identify ways to fund Cancer Moonshot-related research, and consider appropriate partnerships with foundations, academia, professional societies, and the private sector. Specifically, these teams are responsible for:

Discussing approaches and developing initiatives for FY 2018 and FY 2019 that will achieve the goals of the BRP recommendation for which the team is responsible;

Seeking input from the cancer research community, the BRP and its working groups, and NCI advisory committees through workshops, listening sessions, webinars, and other means; and

Providing oversight and coordination of the funded initiatives associated with the BRP recommendation for which the team is responsible.

For more information on the Beau Biden Cancer Moonshot see **https://www.cancer.gov/research/key-initiatives/moonshot-cancer-initiative/implementation.**

The 21st Century Cures Act also authorized the establishment of the FDA OCE (see sidebar on **The Aims of the FDA Oncology Center of Excellence**, p. 99). The OCE is streamlining the work that the FDA does in the field of oncology by bringing together staff from the Center for Drug Evaluation and Research, the Center for Biologics and Evaluation Research, and/or the Center for Devices and Radiological Health. This crosscutting review team design will expedite the evaluation of drugs, biologics, and devices for the treatment of cancer, and thereby help advance the goals of the Beau Biden Cancer Moonshot.

DEVELOPING AND TRAINING THE CANCER WORKFORCE OF TOMORROW

Many of the innovative research questions and fresh ideas come from scientists early in their careers (see sidebar on **Supporting Early-Career Investigators**, p. 50). Ensuring the continued, rapid pace of progress against cancer requires that the next generation of cancer researchers be encouraged, recruited, and supported. A strong pipeline of talented researchers to whom current leaders in the field can pass the baton in the years to come will allow the work to continue in earnest to conquer this disease.

The current generation of early-career investigators has been privy to the exciting advancements that have been thus far described. At the same time, they came of age in a decade when the NIH budget declined by 25 percent, when adjusted for inflation, and the path forward was uncertain. Even though the funding landscape has improved in the past two years, many young investigators saw the stagnant budgets of prior years and opted for alternative career paths, thereby putting future generations of innovative research in jeopardy.

Our country must continue to invest in the education and training of scientists at all career levels, but especially at the dawn of their careers. The cancer workforce of tomorrow also must reflect the increasing diversity in our country, including disciplinary, gender, racial, ethnic, and geographic diversity. Robust, sustained, and predictable funding increases for the NIH, coupled with state and private sector-funded programs to assist early-career scientists, play an irreplaceable role in cultivating tomorrow's scientific leaders.

Members of Congress and NIH officials have recognized the importance of supporting scientists early in their careers, and they have taken important steps to assist young investigators through legislative provisions in the 21st Century Cures Act and new policies enacted through

Supporting the Future of Cancer Research

The Next Generation Researchers Initiative was announced by the NIH earlier this year, with the aim of bolstering support for early-stage and mid-career investigators and addressing challenges they face as they begin and sustain independent research careers. With an expressed commitment to doing more to ensure a strong pipeline of researchers, the NIH plans a multipronged approach to boost the number of scientists at these stages that are supported by NIH grants. The initiative will make additional funds available to do the following:

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

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

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

The NIH estimates that this initiative will require $210 million in funding for the first year, and $1.1 billion over five years. Therefore, this is an initiative that is dependent on robust and sustained funding increases for the NIH over the next several years.

CHAIRMAN
TOM COLE

speaking to AACR leaders at the May 4, 2017, Hill Day

"I am very proud that Congress increased NIH's funding by $2 billion in the fiscal year 2017 omnibus spending bill. Congress also passed the 21st Century Cures Act last December, which will build upon and greatly enhance efforts to find cures for diseases such as cancer ..."

Revisions to the Common Rule

The regulations for federally funded research on human subjects, referred to as the Common Rule, were updated in January 2017 (211). The updates, which aim to enhance safeguards for individuals who participate in cancer and other biomedical research while making it easier for scientists to conduct lifesaving research on samples provided by these individuals, include provisions that allow for:

Use of broad but simple consent from patients regarding the storage, maintenance, and secondary research use of identifiable private information and biospecimens.

Collaborative research being undertaken across multiple institutions to be conducted under a single Institutional Review Board.

Most of the updates will become effective in January 2018, except for provisions related to cooperative research, which become effective in January 2020.

the NIH Office of Extramural Research, including the Next Generation Researchers Initiative (see sidebar on **Supporting the Future of Cancer Research**, p. 101).

POLICIES TO ADVANCE PATIENT-CENTERED RESEARCH AND CARE

In addition to supporting science and research, public policies also must support the beneficiaries of this research—the patients. Above all else, access to comprehensive health insurance coverage is critical for all Americans, especially those who have experienced acute and chronic diseases, including the 1.7 million Americans who will be diagnosed with cancer this year, and the 15.5 million cancer survivors. The Affordable Care Act has provided major benefits for those affected by cancer, including a prohibition on the denial of insurance coverage based on preexisting conditions; Medicaid expansion; dependent coverage until age 26; a prohibition on annual and lifetime coverage caps; and coverage of prevention, early detection, treatment, and survivorship services. Any replacement of the current law must retain these provisions that are so vital for cancer prevention, detection, diagnosis, treatment, and survivorship.

Every year, thousands of individuals, including cancer patients and survivors, make the selfless choice to participate in federally funded cancer research so that effective preventive strategies and treatments continue to make a difference in the lives of those affected by cancer. National policies need to support this participation at every level, from protecting information, to covering routine costs of care, to ensuring that the patient experience is taken into consideration.

Current protections based on basic ethical principles for federally funded research involving human subjects stem from the Federal Policy for the Protection of Human Subjects, known as the "Common Rule." Until January 2017, the Common Rule had not been updated since 1991, even though the field of biomedical research had evolved dramatically. However, on January 18, 2017, the U.S. Department of Health and Human Services (HHS) and 15 other federal agencies issued a final update to the rule intended to safeguard individuals who participate in cancer and other biomedical research, while making it easier for scientists to conduct lifesaving research on samples provided by these individuals (see sidebar on **Revisions to the Common Rule**).

THE AACR CALL TO ACTION

During the past two years, Congress has demonstrated a strong, bipartisan commitment to medical research by providing the first consecutive, significant funding increases for the NIH in more than a decade. Because Congress has recognized that medical research is a high national priority, the trajectory of federal funding appropriated for this lifesaving work has now turned a corner and is once again headed in the right direction.

We are at a watershed moment in cancer research, and we cannot allow this positive momentum to be lost. During this time of both unprecedented scientific opportunity and increasing incidence and associated mortality of cancer, Congress must continue to provide robust, sustained, and predictable investments in the NIH. Annual increases in the NIH budget, coupled with a funding increase for the FDA in FY 2018 and beyond, will ensure the acceleration of the pace at which we make research discoveries and translate them into advances that will save more lives from cancer.

However, in order for the NIH, FDA, and other vitally important scientific agencies to receive the resources that are essential to make further strides toward defeating cancer and the many other human diseases that afflict so many Americans, it is going to require that Congress negotiate a bipartisan budget deal to raise the discretionary budget caps for FY 2018. The shortsighted and restrictive discretionary spending caps that are in place for FY 2018 as a result of the 2011 Budget Control Act will compromise our nation's ability to further understand the complexities of cancer and postpone the development of lifesaving therapies for patients.

Continued progress against cancer requires the unwavering support of our elected leaders. Therefore, AACR respectfully urges Congress to:

- **Continue to support robust, sustained, and predictable growth of the NIH budget** by providing an increase of $2 billion for NIH in FY 2018, for a total funding level of $36.2 billion.
- **Ensure that funding designated through the 21st Century Cures Act for initiatives and programs, such as the Beau Biden Cancer Moonshot and the FDA Oncology Center of Excellence, is fully appropriated in FY 2018.**
- **Increase the FDA budget in FY 2018 to $2.8 billion, an $80 million increase above its FY 2017 level,** to ensure support for regulatory science and to accelerate the pace of development of medical products that are safe and effective.
- **Negotiate a bipartisan budget deal to raise the discretionary budget caps for FY 2018 and beyond,** which would allow our nation's policy makers to continue to invest in priority areas, such as the biomedical research funded by the NIH.

Congress can help us transform cancer care, save more lives from cancer, spur economic growth, and maintain the position of the United States as the global leader in science and medical research by providing annual funding increases for the NIH, NCI, and FDA that are robust, sustained, and predictable. Most importantly, this will continue to bring real hope to the millions of people all over the world whose lives are touched by cancer.

APPENDIX

GLOSSARY*

Acute myeloid leukemia (AML) The most common type of leukemia (blood cancer) diagnosed in the United States. AML is 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 to lower the risk that the cancer will come back. Adjuvant therapy may include chemotherapy, radiation therapy, hormone therapy, targeted therapy, or immunotherapy.

Ampullary cancer A rare cancer that forms in the ampulla of Vater (an enlargement of the ducts from the liver and pancreas where they join and enter the small intestine). Also, called ampulla of Vater cancer.

Anaplastic lymphoma receptor tyrosine kinase (ALK) The ALK gene makes the ALK protein, which is found on the surface of some cells. The protein can initiate a variety of signaling pathways (see Signaling pathway/signaling network), causing proliferation of the cells on which it is found. The ALK gene is altered in several types of cancer, including some non–small cell lung cancers (see Non–small cell lung cancer), some neuroblastomas, and some lymphomas—in particular, anaplastic large cell lymphomas.

Biomedical inflation Biomedical inflation is calculated using the annual change in the Biomedical Research and Development Price Index (BRDPI), which indicates how much the NIH budget must change to maintain purchasing power. In general, the biomedical inflation rate outpaces the economy-wide inflation rate.

BRAF The BRAF protein is generated from the BRAF gene. It is found inside certain cell types, where it is involved in sending signals that direct cell proliferation. Mutations in the BRAF gene have been associated with various cancers, including some non-Hodgkin lymphomas, colorectal cancers, melanomas, thyroid cancers, and lung cancers.

BRCA1/2 (Breast Cancer Resistance Genes 1 and 2) Genes that produce proteins that are involved in repairing damaged DNA. Females who inherit certain mutations (see Mutation) 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 A term for cancers arising in the cervix (the area where the uterus connects to the vagina). The two main types of cervical cancer are squamous cell carcinoma and adenocarcinoma. Most cervical cancers are caused by persistent infection with certain strains of human papillomavirus (HPV; see Human papillomavirus). Normal cells of the cervix do not suddenly become cancerous; they first gradually develop precancerous changes, then later turn into cancer. These changes can be detected by the Papanicolaou (Pap) test and treated to prevent the development of cancer.

Chemotherapy The use of different drugs to kill or slow the growth of cancer cells.

Chromosome Structure within the nucleus of a cell that contains genetic information (DNA) and its associated proteins (see Deoxyribonucleic acid and Epigenetics). Except for sperm and eggs, nearly all nondiseased human cells contain 46 chromosomes.

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 (see Chromosome). Chromosomal translocations can, in some cases, fuel cancer.

Clinical trial A type of research study that tests how well new medical approaches work in people. These studies test new methods for screening, preventing, diagnosing, or treating a disease. Also called clinical study.

Colonoscopy Examination of the inside of the colon using a colonoscope that is inserted into the rectum. A colonoscope is a thin, tube-like instrument with a light and a lens for viewing. It may also have a tool to remove tissue to be checked under a microscope for signs of disease.

Colorectal cancer A group of cancers that start in the colon or the rectum. More than 95 percent of colorectal cancers are adenocarcinomas that arise in cells forming glands that make mucus to lubricate the inside of the colon and rectum. Before a colorectal cancer develops, a growth of tissue or tumor usually begins as a noncancerous polyp on the inner lining of the colon or rectum. Most polyps can be found—for example, through colonoscopy—and removed before they turn into cancer.

Computational biology The development of data-analytical and theoretical methods, mathematical modeling, and computational simulation techniques and their application to the study of biological, behavioral, and social systems.

Computed tomography (CT) A series of detailed pictures of areas inside the body taken from different angles. The pictures are created by a computer linked to an X-ray machine. Also called CAT scan, computerized axial tomography scan, and computerized tomography.

Cyclin-dependent kinases (CDKs) A family of proteins that have important roles in controlling a number of cell processes, including cell multiplication. To function effectively, CDKs must attach to a small protein called a cyclin.

Death rate/mortality rate The number of deaths in a certain group of people in a certain period of time. Death rates may be reported for people who have a certain disease; who live in one area of the country; or who are of a certain gender, age, or ethnic group.

Deoxyribonucleic acid (DNA) The molecules inside cells that carry genetic information and pass it from one generation to the next.

DNA mismatch repair DNA mismatch repair is a system for recognizing and repairing erroneous insertion, deletion, and misincorporation of bases that can arise during DNA replication and recombination, as well as repairing some forms of DNA damage (see Deoxyribonucleic acid).

Drug resistance The failure of cancer cells, viruses, or bacteria to respond to a drug used to kill or weaken them. The cells, viruses, or bacteria may be resistant to the drug at the beginning of treatment or may become resistant after being exposed to the drug.

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.

Endpoint In clinical trials, an event or outcome that can be measured objectively to determine whether the intervention being studied is beneficial. The endpoints of a clinical trial are usually included in the study objectives. Some examples of endpoints are survival, improvements in quality of life, symptom relief, and disappearance of the tumor.

Epidermal growth factor receptor (EGFR) A protein found on the surface of some cells to which epidermal growth factor binds, causing the cells to proliferate. It is found at abnormally high levels on the surface of many types of cancer cells, including many types of lung cancer cells, so these cells may divide excessively in the presence of epidermal growth factor. Also called ErbB1 and HER1.

Epigenetic mark A chemical mark on DNA (see Deoxyribonucleic acid) and histones (see Histone) that can control the accessibility of genes. The collection of epigenetic marks across the entire genome is referred to as the epigenome.

Epigenetics The study of heritable changes in gene expression or cellular phenotype caused by mechanisms other than changes in DNA sequence. Examples of such changes might be DNA methylation or histone deacetylation, both of which serve to suppress gene expression without altering the sequence of the silenced genes.

Five-year survival rate The percentage of people in a specific group, for example, people diagnosed with a certain type of cancer or those who started a certain treatment, who are alive 5 years after they were diagnosed with or started treatment for a disease, such as cancer. The disease may or may not have come back.

Gene The functional and physical unit of heredity passed from parent to offspring. Genes are pieces of DNA (see Deoxyribonucleic acid), and most genes contain the information for making a specific protein.

Glioblastoma A fast-growing type of central nervous system tumor that forms from glial (supportive) tissue of the brain and spinal cord, and has cells that look very different from normal cells. Glioblastoma usually occurs in adults and affects the brain more often than the spinal cord. Also called glioblastoma multiforme, and grade IV astrocytoma.

Head and neck cancer Cancer that arises in the head or neck region, including the nasal cavity, sinuses, lips, mouth, salivary glands, throat, or larynx (voice box).

Helicobacter pylori (H. pylori) A type of bacterium that causes inflammation and ulcers in the stomach or small intestine. People with Helicobacter pylori infections may be more likely to develop cancer in the stomach, including mucosa-associated lymphoid tissue (MALT) lymphoma.

Hepatitis B virus (HBV) A virus that causes hepatitis (inflammation of the liver). It is carried and passed to others through the blood and other body fluids. Different ways the virus is spread include sharing needles with an infected person and being stuck accidentally by a needle contaminated with the virus. Infants born to infected mothers may also become infected with the virus. Although many patients who are infected with HBV may not have symptoms, long-term infection may lead to cirrhosis (scarring of the liver) and liver cancer.

Hepatitis C virus (HCV) A virus that causes hepatitis (inflammation of the liver). It is carried and passed to others through the blood and other body fluids. Different ways the virus is spread include sharing needles with an infected person and being stuck accidentally by a needle contaminated with the virus. Infants born to infected mothers may also become infected with the virus. Although patients who are infected with HCV may not have symptoms, long-term infection may lead to cirrhosis (scarring of the liver) and liver cancer. These patients may also have an increased risk for certain types of non-Hodgkin lymphoma.

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 (see Chromosome). Histones attach to DNA (see Deoxyribonucleic acid) and help control which genes are accessible for reading.

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 (see Cervical cancer). Human papillomaviruses also play 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 incidence rate is defined as the number of new cases per population at risk in a given time period.

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.

Lynch syndrome An inherited disorder in which affected individuals have a higher-than-normal chance of developing colorectal cancer and certain other types of cancer, often before the age of 50. Alterations in several genes involved in DNA mismatch repair have been linked to Lynch syndrome. Also, called hereditary nonpolyposis colon cancer and HNPCC.

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.

Microsatellite instability (MSI) A change that occurs in the DNA of certain cells (such as tumor cells) in which the number of repeats of microsatellites (short, repeated sequences of DNA) is different than the number of repeats that was in the DNA when it was inherited. The cause of microsatellite instability may be a defect in the ability to repair mistakes made when DNA is copied in the cell.

Monoclonal antibody Antibodies are natural proteins made by a type of immune cell called a B cell to help provide protection from pathogens such as bacteria and viruses. The protective effects of an antibody are determined largely by the specific protein to which it attaches. Researchers have developed ways to generate large quantities of identical antibodies, so called monoclonal antibodies. They have also developed several ways to use monoclonal antibodies to treat some types of cancer.

Mutation Any change in the DNA (see Deoxyribonucleic acid) 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 research-focused institutes and centers of the National Institutes of Health. The NCI coordinates the National Cancer Program, which conducts and supports research, training, health information dissemination, and other programs with respect to the cause, diagnosis, prevention, and treatment of cancer; rehabilitation from cancer; and the continuing care of cancer patients and their families.

Neuroendocrine tumors Rare types of cancer that form from cells that release hormones into the blood in response to a signal from the nervous system. Neuroendocrine tumors can occur anywhere in the body, although most frequently they arise in the lungs, appendix, small intestine, rectum, and pancreas.

Non–small cell lung cancer (NSCLC) A group of lung cancers that are named for the kinds of cells found in the cancer and how the cells look under a microscope. The three main types of NSCLC are squamous cell carcinoma, large cell carcinoma, and adenocarcinoma. NSCLC is the most common kind of lung cancer.

Oncology The branch of medicine that focuses on cancer diagnosis and treatment.

Ovarian cancer Cancer that forms in tissues of the ovary (one of a pair of female reproductive glands in which the ova, or eggs, are formed). Most ovarian cancers are either ovarian epithelial cancers (cancer that begins in the cells on the surface of the ovary) or malignant germ cell tumors (cancer that begins in egg cells).

Platinum-based chemotherapy Treating cancer using chemotherapeutic agents that are coordination complexes of platinum. These drugs are used to treat almost 50 percent of cancer patients. Popular among these drugs are cisplatin and carboplatin, but several have been proposed or are under development.

Polyp A benign growth that protrudes from a mucous membrane, most typically associated with the colon.

Precision cancer medicine The tailoring of treatments to the individual characteristics—in particular, the genetics—of each patient and her or his cancer. Also called personalized cancer medicine, molecularly based cancer medicine, individualized cancer medicine, tailored cancer medicine, and genetic cancer medicine.

Programmed death-1 (PD-1) A protein on the surface of immune cells called T cells (see T cell). When PD-1 attaches to programmed death-ligand 1 (PD-L1) on other cells (see Programmed death-ligand 1), 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 (see Programmed death-1 and T cell).

Prostate cancer A form of cancer that starts in tissues of the prostate (a gland in the male reproductive system found below the bladder and in front of the rectum). In men, it is the most frequently diagnosed cancer and the second most common cause of death from cancer.

Prostate-specific antigen (PSA) A protein secreted by the prostate gland, increased levels of which are found in the blood of patients with cancer of the prostate.

Protein A molecule made up of amino acids that is needed for the body to function properly.

Radiation Energy released in the form of particle or electromagnetic waves. Common sources of radiation include radon gas, cosmic rays from outer space, medical X-rays, and energy given off by a radioisotope (unstable form of a chemical element that releases radiation as it breaks down and becomes more stable).

Radiotherapy The use of high-energy radiation from X-rays, gamma rays, neutrons, protons, and other sources to kill cancer cells and shrink tumors. Radiation may come from a machine outside the body (external-beam radiation therapy), or it may come from radioactive material placed in the body near cancer cells (internal radiation therapy). Systemic radiotherapy uses a radioactive substance, such as a radiolabeled monoclonal antibody, that travels in the blood to tissues throughout the body. Also called irradiation and radiation therapy.

Receptor A protein in a cell that attaches to specific molecules, such as hormones, from outside the cell, in a lock-and-key manner, producing a specific effect on the cell—for example, initiating cell proliferation. Receptors are most commonly found spanning the membrane surrounding a cell but can be located within cells.

Signaling pathway/signaling network A group of molecules in a cell that work together to control one or more cell functions, such as cell proliferation or cell death. After the first molecule in a pathway receives a signal, it alters the activity of another molecule. This process is repeated until the last molecule is activated and the cell function involved is carried out. Abnormal activation of signaling pathways can lead to cancer, and drugs are being developed to block these pathways. These drugs may help prevent cancer cell growth and kill cancer cells.

Soft tissue sarcoma A group of cancers that arise in soft tissues of the body such as the muscles, tendons, fat, blood vessels, lymph vessels, nerves, and tissues around joints. Both children and adults can develop soft tissue sarcomas. Rhabdomyosarcoma is the most common type of soft tissue sarcoma in children, while gastrointestinal stromal tumors are the most common in adults.

Standard of care The intervention or interventions generally provided for a certain type of patient, illness, or clinical circumstance. The intervention is typically supported by evidence and/or expert consensus as providing the best outcomes for the given circumstance.

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.

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.

Urothelial carcinoma The most common type of bladder cancer. It begins in urothelial cells that line the inside of the bladder. These cells are able to change shape and stretch when the bladder is full.

Vaccine A substance or group of substances meant to cause the immune system to respond to a tumor or to microorganisms such as bacteria or viruses. A vaccine can help the body recognize and destroy cancer cells or microorganisms.

*This list contains some of the specialized terms pertinent to the *AACR Cancer Progress Report 2017*.

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 leukemias	idarubicin	Idamycin PFS
Multiple cancers	ifosfamide	Ifex
Colon, lung, and rectal cancers	irinotecan	Camptosar; Campostar
Pancreatic cancer	irinotecan liopsome injection	Onivyde
Brain tumors	lomustine	CeeNU
Multiple cancers	mechlorethamine hydrochloride	Mustargen
Multiple cancers	melphalan	Alkeran
Certain lymphomas	methoxsalen	Uvadex
Multiple cancers	mitoxantrone	Novantrone
Colon cancer	oxaliplatin	Eloxatin
Testicular cancer	plicamycin	Mithracin
Certain lymphomas	procarbazine	Matulane
Pancreatic cancer	streptozocin	Zanosar
Melanoma; certain brain cancers	temozolomide	Temodar
Certain leukemias	thioguanine	Thioguanine Tabloid
Multiple cancers	thiotepa	Thioplex
Ovarian and small cell lung cancers	topotecan	Hycamtin
Colorectal cancer	trifluridine AND tipiracil	Lonsurf
Bladder cancer	valrubicin	Valstar

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Cell Cytoskeleton–modifying Agents

Approved Indication	Generic Name	Trade Name
Prostate cancer	cabazitaxel	Jevtana
Multiple cancers	docetaxel	Taxotere
Breast cancer; liposarcoma	eribulin mesylate	Halaven
Breast cancer	ixabepilone	Ixempra
Multiple cancers	paclitaxel	Taxol
Breast, lung, and pancreatic cancers	paclitaxel albumin-bound particles	Abraxane
Multiple cancers	vinblastine	Velban
Certain leukemias and lymphomas	vincristine	Oncovin
Certain leukemias and lymphomas	vincristine sulfate liposomes	Marqibo
Breast and lung cancers	vinorelbine tartrate	Navelbine

Antinutrients

Approved Indication	Generic Name	Trade Name
Certain leukemias	asparaginase	Elspar; Kidrolase

Gene-transcription Modifiers

Approved Indication	Generic Name	Trade Name
Certain lymphomas	bexarotene	Targretin
Liposarcoma and leiomyosarcoma	trabectedin	Yondelis
Certain leukemias	tretinoin (all-trans retinoic acid)	Vesanoid

Supplemental Table 2
(continued)

FDA-approved Therapeutics for the Treatment of Cancer

Radiation-emitting Drugs

Approved Indication	Generic Name	Trade Name
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	bicalutamide	Casodex
Prostate cancer	degarelix	Firmagon
Prostate cancer	enzalutamide	Xtandi
Prostate cancer	estramustine	Emcyt; Estracyt
Breast cancer	exemestane	Aromasin
Prostate cancer	flutamide	Eulexin
Metastatic breast cancer	fulvestrant	Faslodex
Prostate and breast cancers	goserelin acetate implant	Zoladex
Breast cancer	letrozole	Femara
Prostate cancer	leuprolide acetate	Eligard; Lupron: Viadur
Breast and endometrial cancers	megestrol acetate	Megace; Megace Oral Suspension
Breast cancer	tamoxifen	Nolvadex
Prostate cancer	triptorelin pamoate	Trelstar Depot

Immune-system Modifiers

Approved Indication	Generic Name	Trade Name
Multiple cancers	interferon alfa-2b	Intron A
Melanoma; kidney cancer	aldesleukin	Proleukin
Myelodysplastic syndrome; certain lymphomas	lenalidomide	Revlimid
Multiple myeloma	pomalidomide	Pomalyst

Proteosome Inhibitors

Approved Indication	Generic Name	Trade Name
Multiple myeloma	bortezomib	Velcade
Multiple myeloma	carfilzomib	Kyprolis
Multiple myeloma	ixazomib	Ninlaro

Protein-translation Inhibitors

Approved Indication	Generic Name	Trade Name
Certain type of leukemia	omacetaxine mepesuccinate	Synribo

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Epigenome-modifying Agents

Approved Indication	Generic Name	Trade Name
Myelodysplastic syndrome	azacitidine	Vidaza
Certain lymphomas	belinostat	Beleodaq
Myelodysplastic syndrome	decitabine	Dacogen
Multiple myeloma	panobinostat	Farydak
Certain lymphomas	romidepsin	Istodax
Certain lymphomas	vorinostat	Zolinza

DNA-repair Inhibitors

Approved Indication	Generic Name	Trade Name
Certain types of ovarian, fallopian tube, and primary peritoneal cancer	niraparib	Zejula
Certain form of ovarian cancer*	olaparib	Lynparza
Certain type of ovarian cancer	rucaparib*	Rubraca

Immune-checkpoint Inhibitors

Approved Indication	Generic Name	Trade Name
Certain type of bladder cancer and lung cancer	atezolizumab	Tecentriq
Certain types of bladder cancer and skin cancer	avelumab	Bavencio
Certain type of bladder cancer	durvalumab	Imfinzi
Melanoma	ipilimumab	Yervoy
Multiple cancers	nivolumab	Opdivo
Multiple cancers	pembrolizumab	Keytruda

Bone-remodeling Inhibitors

Approved Indication	Generic Name	Trade Name
Potentially lethal complication of advanced cancers*	denosumab	Xgeva

Angiogenesis Inhibitors

Approved Indication	Generic Name	Trade Name
Kidney cancer	axitinib	Inlyta
Multiple cancers	bevacizumab	Avastin
Thyroid cancer; kidney cancer	cabozantinib	Cometriq; Cabometyx
Certain type of thyroid cancer; kidney cancer	lenvatinib	Lenvima
Kidney cancer; soft tissue sarcomas; gastrointestinal stromal tumors	pazopanib	Votrient
Certain types of lung and stomach cancers	ramucirumab	Cyramza
Colorectal cancer; gastrointestinal stromal tumors and liver cancer	regorafenib	Stivarga
Kidney cancer; certain type of thyroid cancer	sorafenib	Nexavar

Supplemental Table 2
(continued)

FDA-approved Therapeutics for the Treatment of Cancer

Angiogenesis Inhibitors *(continued)*

Approved Indication	Generic Name	Trade Name
Gastrointestinal stromal tumors; kidney cancer; some pancreatic cancers	sunitinib	Sutent
Thyroid cancer	vandetanib	Caprelsa
Colorectal cancer	ziv-aflibercept	Zaltrap

Cell-lysis Mediators

Approved Indication	Generic Name	Trade Name
Certain leukemias	alemtuzumab	Campath
Certain types of leukemia	blinatumomab	Blincyto
Certain lymphomas	brentuximab vedotin	Adcetris
Multiple myeloma	daratumumab	Darzalex
Neuroblastoma	dinutuximab	Unituxin
Multiple myeloma	elotuzumab	Empliciti
Certain lymphomas	ibritumomab	Zevalin
Certain form of leukemia; certain form of lymphoma	obinutuzumab	Gazyva
Certain leukemias	ofatumumab	Arzerra
Certain lymphomas	rituximab	Rituxan

Oncolytic Virus

Approved Indication	Generic Name	Trade Name
Melanoma	talimogene laherparepvec^	Imlygic

Therapeutic Vaccines

Approved Indication	Generic Name	Trade Name
Prostate cancer	sipuleucel-T	Provenge

Cell-signaling Inhibitors

Approved Indication	Generic Name	Trade Name
HER2+ breast cancer	ado-trastuzumab emtansine	Kadcyla
Certain type of lung cancer	afatinib	Gilotrif
Certain form of lung cancer	alectinib	Alecensa
Certain type of leukemia	bosutinib	Bosulif
Certain type of 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
Specific lung cancers*	crizotinib	Xalkori
Certain type of melanoma* and lung cancer*	dabrafenib	Tafinlar
Some leukemias	dasatinib	Sprycel
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 form of lymphoma and non-Hodgkin lymphoma	ibrutinib	Imbruvica
Certain types of leukemia and lymphoma	idelalisib	Zydelig
Some leukemias; stomach cancer; certain type of skin cancer	imatinib	Gleevec; Glivec
HER2+ breast cancers	lapatinib	Tykerb
Certain types of leukemia	midostaurin*	Rydapt
Certain form of lung cancer	necitumumab	Portrazza
Certain type of breast cancer	neratinib	Nerlynx
Some leukemias	nilotinib	Tasigna
Soft tissue sarcoma	olaratumab	Lartruvo
Certain form of lung cancer*	osimertinib	Tagrisso
Certain subtype of breast cancer	palbociclib	Ibrance
Colon cancer	panitumumab	Vectibix
HER2+ breast cancer	pertuzumab	Perjeta
Certain types of leukemia	ponatinib	Iclusig
Certain type of breast cancer	ribociclib	Kisqali
Myelofibrosis	ruxolitinib	Jakafi
Most common type of skin cancer	sonidegib	Odomzo
Certain types of melanoma* and lung cancer*	trametinib	Mekinist
HER2+ breast cancer	trastuzumab	Herceptin
Kidney cancer	temsirolimus	Toricel; Torisel
Thyroid cancer	vandetanib	Caprelsa
Melanoma*	vemurafenib	Zelboraf
Most common type of skin cancer	vismodegib	Erivedge

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* 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

Surgical Treatments

Used to Treat	Procedure
Breast cancer	Mastectomy
Breast cancer	Lumpectomy
Testicular cancer	Orchiectomy
Multiple head, neck, and chest cancers	Video-Assisted Thoracoscopic Surgery (VATS)
Variety of abdominal cancers	Laparoscopic surgery
Sarcoma and other cancers	Reconstructive and limb-sparing surgeries
Kidney cancer	Partial nephrectomy
Pancreatic cancer	The Whipple/modified Whipple procedure
Stomach-sparing pancreatic surgery for pancreatic cancer	Pancreatoduodenectomy
Rectal cancer	Total mesorectal excision
Prostate cancer	Nerve-sparing prostatectomy
Rectal cancer	Transanal Endoscopic Microsurgery (TEM)
Testicular cancer	Modified retroperitoneal lymph node dissection
Breast, melanoma, and colorectal cancers	Sentinel lymph node biopsies
Breast cancer, laryngeal cancer , and anal/rectal cancer	Neoadjuvant chemotherapy
Multiple cancers	Robotic or computer-assisted surgeries

Radiotherapy Treatments

Used to Treat	Procedure
Prostate, cervical, other cancers	Brachytherapy
Multiple cancers	Image-guided radiation therapy (IGRT)
Multiple cancers	Intensity Modulated Radiation Therapy (IMRT)
Brain metastases	Stereotactic radiosurgery
Liver and lung cancers	Stereotactic body radiation therapy
Multiple cancers	Neoadjuvant and adjuvant radiotherapy combined with radiation therapy
Head and neck cancers	Radiation therapy combined with molecularly targeted therapy (cetuximab)
Prostate cancer	Radiation therapy combined with androgen deprivation
Prostate cancer	Adjuvant radiotherapy
Pediatric cancers	Proton therapy
Unresectable glioblastoma, lung cancer, head and neck cancer, esophageal cancer, pancreatic cancer	Concurrent chemotherapy and radiation therapy
Anal cancer, head and neck cancer	Radiation with chemotherapy can produce cure with organ preservation
Breast cancer	Radiation and surgery (with or without chemotherapy) can produce cure with organ preservation

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