AACR American Association for Cancer Research

FINDING CURES TOGETHER℠








AACR CANCER PROGRESS REPORT **2016**



Saving Lives Through Research

CancerProgressReport.org \ AACR.org \ #CancerProgress16

AACR American Association for Cancer Research
FINDING CURES TOGETHER℠

AACR CANCER PROGRESS REPORT **2016**

Saving Lives Through Research

CancerProgressReport.org \ AACR.org \ #CancerProgress16

Please cite this report as:
American Association for Cancer Research. AACR Cancer Progress Report 2016. Clin Cancer Res 2016;22 (Supplement 1):SI-S137.

TABLE OF CONTENTS

AACR CANCER PROGRESS REPORT 2016 STEERING COMMITTEE

Nancy E. Davidson, MD
Chairperson
AACR President 2016–2017
Director
University of Pittsburgh Cancer Institute
Pittsburgh, Pennsylvania

Scott A. Armstrong, MD, PhD
Chair
Department of Pediatric Oncology
Dana-Farber Cancer Institute
Boston, Massachusetts

Lisa M. Coussens, PhD
Associate Director for Basic Research
OHSU Knight Cancer Institute
Portland, Oregon

Marcia R. Cruz-Correa, MD, PhD
Associate Professor of Medicine,
Biochemistry, and Surgery
University of Puerto Rico
Comprehensive Cancer Center
San Juan, Puerto Rico

Ralph J. DeBerardinis, MD, PhD
Chief
Division of Pediatric Genetics and Metabolism
UT Southwestern Medical Center
Dallas, Texas

James H. Doroshow, MD*
Director
Division of Cancer Treatment and Diagnosis
National Cancer Institute
Bethesda, Maryland

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

** This author contributed to the development and review of this manuscript but is unable to endorse the request for NIH funding.*

Patrick Hwu, MD
Chair
Department of Melanoma Medical Oncology
The University of Texas MD Anderson Cancer Center
Houston, Texas

Thomas W. Kensler, PhD
Professor
Department of Pharmacology and Chemical Biology
University of Pittsburgh
Pittsburgh, Pennsylvania

Monica Morrow, MD
Chief
Breast Service, Department of Surgery
Memorial Sloan Kettering Cancer Center
New York, New York

Charles G. Mulligan, MSc, MD
Co-Leader
Hematological Malignancies Program
St. Jude Children's Research Hospital
Memphis, Tennessee

William Pao, MD, PhD
Global Head
Oncology Discovery and Translational Area
Roche Pharma Research and Early Development
Basel, Switzerland

Elizabeth A. Platz, MPH, ScD
Deputy Director
Department of Epidemiology
Johns Hopkins Bloomberg School of Public Health
Baltimore, Maryland

Thomas J. Smith, MD
Harry J. Duffey Family Professor of Palliative Medicine
Johns Hopkins Medicine
Baltimore, Maryland

Cheryl L. Willman, MD
Director & CEO
University of New Mexico
Comprehensive Cancer Center
Albuquerque, New Mexico

AACR STAFF

Shawn M. Sweeney, PhD
Project Lead
Associate Director, Translational Research
Philadelphia, Pennsylvania

Karen Honey, PhD
Lead Science Writer
Project Co-lead
Senior Managing Editor, Science Communications
Philadelphia, Pennsylvania

Brenna L. Adams
Lead Designer
Special Publications Designer
Philadelphia, Pennsylvania

Paul J. Driscoll, Jr.
Senior Director, Marketing and Creative Services
Philadelphia, Pennsylvania

Joshua F. Goldstein
Director, Brand Strategy Communications
Philadelphia, Pennsylvania

James A. Ingram II
Assistant Director, Government Relations and Advocacy
Washington, DC

Mary Anne Mennite
Executive Editor and Senior Liaison to the CEO
Philadelphia, Pennsylvania

Jon G. Retzlaff, MBA, MPA
Managing Director, Science Policy and Government Affairs
Washington, DC

Anna B. Sadusky, PhD
Associate Director, Regulatory Science and Policy
Washington, DC

Shimere Williams Sherwood, PhD
Associate Director, Health Policy
Washington, DC

Mary Lee Watts, MPH, RD
Director, Government Relations and Advocacy
Washington, DC

Nicolle Rager Fuller
Illustrator
Sayo-Art, LLC
Bellingham, Washington

A MESSAGE FROM THE AACR

It is a tremendously exciting time for the cancer community. Thanks to research, we are making significant progress against the many diseases we call cancer. More people than ever before are living longer and fuller lives after a cancer diagnosis. In fact, the number of children and adults living in the United States with a history of cancer rose by 1 million from 2014 to 2016, reaching a record 15.5 million. Moreover, there has been a renewed, bipartisan commitment from Congress and the Administration to prioritize biomedical science and cancer research. In December 2015, members of the U.S. House and Senate came together to agree to a $2 billion increase in the National Institutes of Health (NIH) budget for fiscal year 2016. Then, in January 2016, President Obama announced that Vice President Biden would lead a "National Cancer Moonshot Initiative." These actions have touched off an unprecedented national and international dialogue about cancer and re-enforced the importance of research for improving health and saving lives from cancer.

The *AACR Cancer Progress Report 2016* adds important perspective to the dialogue by highlighting how research, much of which is supported by federal investments in the NIH and National Cancer Institute (NCI), powers the development of new and better ways to prevent, detect, diagnose, treat, and cure some types of cancer. This progress is improving lives around the world—for example, the lives of the 15 courageous men, women, and children who shared their personal experiences with cancer in this report. The AACR is extremely grateful to these inspiring individuals because their stories, coupled with the advances described herein, provide enormous hope for a much brighter future for cancer patients and their loved ones.

Seven of the anticancer therapeutics highlighted in the report harness the power of a patient's immune system to treat his or her cancer (p. 81). These revolutionary treatments are improving survival and quality of life for patients with an increasing number of types of cancer. For example, in January 2015, immunotherapeutics that release certain brakes on the immune system had been approved by the U.S. Food and Drug Administration (FDA) for treating just one type of cancer—melanoma. As of July 31, 2016, they have been approved for treating five types of cancer—bladder cancer, Hodgkin lymphoma, kidney cancer, lung cancer, and melanoma—and more approvals are anticipated in the near future.

The development of immunotherapeutics was made possible by dedicated researchers integrating scientific discoveries in the fields of immunology and cancer biology. Historically, researchers working in these two fields tended to work independently, but by coming together, they spurred the development of powerful new approaches to cancer treatment. As we increase the diversity of scientific disciplines represented in the cancer research effort—for example, by including those working in nonbiological disciplines such as physical, chemical, engineering and mathematical sciences, as well as computational biology and bioinformatics—we will be in a position to make even more breakthroughs in cancer research.

Discoveries in the field of cancer genomics wrought by collaborative teams of researchers in the fields of cancer genomics, computational biology, and bioinformatics have already led to numerous anticancer therapeutics that more precisely target cancer than the treatments that have been the mainstay of cancer care for decades, such as cytotoxic chemotherapy and radiotherapy. Further collaboration from additional specialties will further enhance our ability to exploit the enormous amounts of genomic information available for the benefit of cancer patients around the world.

Collaboration has been a mainstay of biomedical research, and new and innovative methods of collaborating are currently being explored. Among the new initiatives that aim to harness the power of collaboration is AACR Project Genomics, Evidence, Neoplasia, Information, Exchange (GENIE). AACR Project GENIE is an international cancer registry built by sharing clinical cancer sequencing data from eight international institutions that are global leaders in genomic sequencing for clinical utility. By collecting, cataloging, and linking tumor genetic data with data on patient outcomes from all participating institutions and then making the data publicly available, AACR Project GENIE will facilitate clinical decision making and catalyze new clinical and translational cancer research.

Vice President Biden, who oversees the National Cancer Moonshot Initiative, has said that he sees increased data sharing and collaboration as keys to achieving the goal of the National Cancer Moonshot Initiative, which is to bring about a decade's worth of advances in cancer prevention, early detection, and treatment in 5 years.

We have never been better poised to realize this goal than we are now. We have the scientific knowledge and capability to deliver advances across the continuum of cancer care

and a commitment from the U.S. government to remove barriers to progress and to forge the partnerships necessary to make this a reality.

However, the revitalized commitment from the U.S. government to making research a national priority comes after the biomedical research community has faced more than a decade of stagnant federal investments in the NIH and NCI. Thus, the AACR urges Congress and the Administration to ensure that the NIH, NCI, and U.S. Food and Drug Administration (FDA) receive robust, sustained, and predictable budget increases each year and that the National Cancer Moonshot Initiative is strongly supported with the new funds required to ensure its success. In addition, elected leaders must readjust the current discretionary budget caps upward to allow for healthy and lasting growth in the annual funding levels for the NIH, NCI, and FDA.

The AACR calls upon all its members and indeed all Americans to join us in our goal to make cancer research a long-term national priority. By all of us working together we can seize these unprecedented scientific opportunities and make strides to eradicate cancer worldwide.

Nancy E. Davidson, MD

AACR President

Margaret Foti, PhD, MD (hc)

AACR Chief Executive Officer

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 to prevent and cure all cancers. AACR membership includes 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, detection, 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 nearly 19,500 attendees. In addition, the AACR publishes eight prestigious, peer-reviewed scientific journals and a magazine for cancer survivors, patients, and their caregivers. The AACR funds meritorious research directly as well as in cooperation with numerous cancer organizations. As the Scientific Partner of Stand Up To Cancer, the AACR provides expert peer review, grants administration, and scientific oversight of team science and individual investigator grants in cancer research that have the potential for near-term patient benefit. The AACR actively communicates with legislators and other policymakers 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 powers progress against cancer by increasing our understanding of the collection of diseases we call cancer and by allowing us to translate this knowledge into new and increasingly precise ways to prevent, detect, diagnose, treat, and cure a number of these diseases.

AACR PRESIDENT, 2016–2017
NANCY E. DAVIDSON, MD

> "Everything we know today about how to take care of people with cancer is built on decades of research."

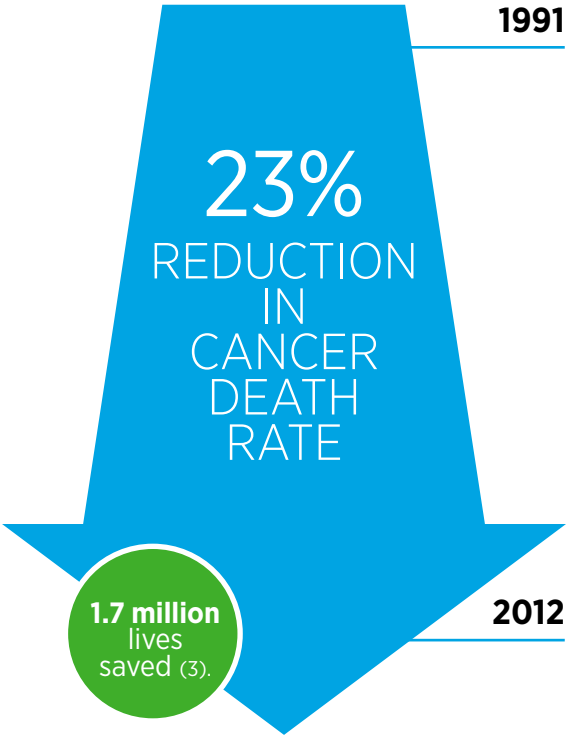
Much of the research is made possible by investments from the U.S. federal government administered through the National Institutes of Health (NIH), in particular its largest institute, the National Cancer Institute (NCI). Federal funding of the U.S. Food and Drug Administration (FDA) is also important because it helps speed the approval of safe and effective treatments, such as anticancer therapeutics.

As the first and largest cancer 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 committed to increasing public understanding of cancer and the importance of cancer research to public health, as well as to advocating for increased federal funding for the NIH, NCI, and 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 sixth edition of the report highlights how research continues to improve lives, like the lives of the 15 courageous individuals featured in this report who have shared their experiences with cancer. It also underscores how unwavering, bipartisan support from Congress and the Administration, in the form of robust and sustained increases in funding for the NIH, NCI, and FDA, is vital if we are to accelerate the pace of progress against cancer for the benefit of patients and their loved ones everywhere.

CANCER IN 2016

Research is our best defense against cancer. It powers the development of new and better ways to prevent, detect, diagnose, treat, and cure a number of the many diseases we call cancer. These advances are driving down overall U.S. cancer incidence and death rates and increasing the number of children and adults who are living longer, higher quality lives after a cancer diagnosis.



Although we are making extraordinary advances, cancer continues to be an enormous public health challenge globally. In fact, this collection of diseases accounts for one in every seven deaths worldwide and one in every four deaths in the United States. Moreover, as a result of an increase in the number of individuals over the age of 65, among other factors, the number of cancer deaths is

expected to rise dramatically in the coming decades if new and better ways to prevent, detect, diagnose, and treat cancer are not developed. In the United States alone, the number of cancer deaths is predicted to rise from 595,690 in 2016 to 946,833 in 2030.

Fueling the projected increase in the number of cancer deaths will be a rise in the number of cancer diagnoses, which will, in turn, drive up the costs of cancer. In fact, it is estimated that the direct medical costs of cancer care in the United States will rise to $156 billion in 2020, from nearly $125 billion in 2010. When these costs are compared to the total NCI budget for fiscal year 2016, which is just $5.21 billion, it is clear that the research powering progress against cancer is a vital national investment.

PREVENTING CANCER FROM DEVELOPING

Decades of research have led to the identification of numerous factors that increase a person's risk of developing cancer. Given that exposure to many of these factors can be eliminated or reduced, 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 notable 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 (HPV).

75%

of U.S. lung cancer cases could be prevented through elimination of cigarette smoking (27).

Although 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, some individuals continue to expose themselves to these risk factors. Thus, a great deal more research and more resources are needed to understand how best to help these individuals eliminate or reduce their risk of some cancers.

FINDING CANCER

Not all cases of cancer are attributable to preventable causes. As a result, cancer screening tests that can identify a precancer or cancer early in development, when it can be more easily and successfully treated, are an important part of health care.

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 whether the test is covered by his or her health insurance are also important considerations. Therefore, every individual should consult with his or her health care practitioners to develop a cancer prevention and early detection plan tailored to his or her situation.

As we develop and implement new strategies that pair increased molecular understanding of cancer development with knowledge of an individual's unique cancer risk profile, we will move closer to a new era of precision cancer prevention and early detection.

SAVING LIVES THROUGH RESEARCH

The hard work of individuals throughout the biomedical research cycle constantly powers the translation of discoveries to advances across the clinical cancer care continuum. These advances are improving survival and quality of life for people around the world.

As a result of research advances, the FDA approved 13 new therapeutics for treating certain types of cancer, one new cancer screening test, one new diagnostic test, two new diagnostic imaging agents, and a new medical device in the 12 months leading up to July 31, 2016. During this time, the FDA also approved new uses for 11 previously approved anticancer therapeutics.

Four 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 **Ginger Tam** (p. 72).

Another four of the new anticancer therapeutics are immunotherapeutics that are yielding remarkable and durable patient responses, as highlighted in the report by the experiences of **Dave Maddison** and **Bob Ribbans** (p. 88 and 94, respectively). Importantly, immunotherapeutics have been shown to benefit patients with an increasingly diverse array of types of cancer. For example, one immunotherapeutic, nivolumab (Opdivo), was approved by the FDA for use as a treatment for three different types of cancer in just 6 months.

Research-fueled advances in cancer detection, diagnosis, and treatment are helping more and more people to survive longer and lead fuller lives after a cancer diagnosis. Despite this progress, cancer survivors often face serious and persistent adverse outcomes, including physical, emotional, psychosocial, and financial challenges as a result of their disease and treatment. Palliative care, given alongside cancer treatment and through the balance of life, is one approach that can improve quality of life for patients and survivors. Much more research is needed, however, to identify new and better ways to help cancer survivors meet the numerous challenges that they face.

ANTICIPATING FUTURE PROGRESS

Research is the foundation on which progress against cancer is made. As we look to the future, researchers throughout the cycle of biomedical research, including **AACR President Nancy E. Davidson, MD** (p. 102), are striving to accelerate the pace of lifesaving progress.

Cancer genomics research, which has been central to the precision medicine revolution, is one area in which the pace of progress is expected to accelerate in the future. This type of research promises to dramatically increase the number of potential targets for the development of novel molecularly targeted anticancer therapeutics and to identify markers that determine which patients are most likely to respond to a particular treatment.

As our knowledge of cancer biology grows, it is becoming increasingly clear that we cannot study cancer in isolation. We need to know more about the whole person in which the cancer has developed. This knowledge is particularly vital for powering progress in the emerging area of precision cancer prevention.

BUILDING BLOCKS OF FURTHER PROGRESS AGAINST CANCER

Federal investments in the NIH, NCI, and FDA have powered extraordinary progress against cancer by catalyzing scientific discovery 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 dramatically 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 save lives. To do this, we must ensure that robust, sustained, and predictable federal funding is provided for biomedical research, cancer research, and regulatory science. We must also provide strong support for cross-cutting initiatives like the National Cancer Moonshot Initiative and the Precision Medicine Initiative. Only by investing in research talent, tools, and infrastructure; supporting regulatory science initiatives; and increasing patient involvement in precision medicine initiatives, will we be able to accelerate the pace of progress and realize our goal of preventing and curing cancer.

Cancer genomics research will pinpoint new potential targets for anticancer therapeutics.

VICE PRESIDENT JOE BIDEN
AACR ANNUAL MEETING, APRIL 20, 2016.

> Today, cancer is the leading cause of death worldwide. And that's only expected to increase in the coming decades—unless we make more progress today. I know we can.

CALL TO ACTION

Late last year, as the fiscal year (FY) 2016 appropriations bill was being finalized, a bipartisan majority of members of Congress called for a significant funding increase for the NIH. The result was a $2 billion budget increase for the NIH in FY 2016, the agency's first significant annual funding boost in more than a decade.

During Senate debate on this year's (FY 2017) appropriations bill that provides funding to the NIH, Senator Roy Blunt (R-MO), Chairman of the Senate Appropriations Subcommittee on Labor, Health and Human Services, Education, and Related Agencies, stated, "Last year, I made clear that sustained funding was as important as the increased investment. A pattern begins in the second year, and we have seized the opportunity this year to begin a pattern of increases for the NIH." Chairman Blunt backed up his words by proposing another $2 billion funding increase for the NIH in FY 2017.

The AACR is supportive of Senator Blunt's statement and action in his role as Subcommittee Chairman, especially because of the unprecedented scientific opportunities that exist today to improve the way we prevent, detect, diagnose, and treat cancer. Robust, sustained, and predictable investments in medical research, coupled with comparable funding increases for the FDA, will accelerate progress against cancer at this critical time in the cancer field.

The AACR also applauds Vice President Joe Biden's comprehensive proposal for preventing cancer and accelerating the discovery of new cancer treatments through the National Cancer Moonshot Initiative. This timely initiative has galvanized the cancer community and sparked a renewed dialogue on how we can speed the pace of progress for the benefit of all patients with cancer. Working together, we can capitalize on this unique moment in cancer research to harness the extraordinary knowledge obtained through past federal investments like the Human Genome Project, and allow for the translation of this information into strategies to prevent, detect, and treat cancer and a myriad of other diseases.

Therefore, the AACR respectfully urges Congress and the Administration to:

- **Support the Senate Appropriations Labor, Health and Human Services, Education, and Related Agencies Subcommittee's FY 2017 bill, which proposes to provide an increase of $2 billion for the NIH in FY 2017.**
- **Finalize a Senate version of the House-passed 21st Century Cures Act that includes crucial funding for the NIH to support the National Cancer Moonshot Initiative and other important strategic research initiatives.**
- **Support an FDA budget in FY 2017 of $2.85 billion, $120 million above its FY 2016 level, to ensure support for regulatory science and the timely approval of therapeutics that are safe and effective.**
- **Readjust the discretionary budget caps for FY 2018 and beyond, which would allow our nation's policymakers to continue to provide robust, sustained, and predictable funding increases for the NIH, NCI, and FDA in future years.**

By taking such actions, we will improve our nation's health, sustain our leadership in cancer research and biomedical science, and spur our innovation-based economy.

A SNAPSHOT OF A YEAR OF PROGRESS

2016

Today, **1 in 21 people** is a cancer survivor

15.5 MILLION SURVIVORS

112,370 of these individuals are children or adolescents

In 1971, **1 in 69 people** was a cancer survivor

3 MILLION SURVIVORS

1971

BETWEEN AUG. 1, 2015, AND JULY 31, 2016, THE FDA APPROVED:

- 13 **new** anticancer therapeutics.
- 11 **new uses** for previously approved anticancer therapeutics.
- 1 **new** diagnostic test.
- 1 **new** cancer screening test.
- 2 **new** diagnostic imaging agents.
- 1 **new** medical device.

RESEARCH CONTINUES TO ADVANCE IMMUNOTHERAPY

Leading to four new immunotherapeutics being approved by the FDA. Three of these four treatments are:

effectively treating patients with bladder cancer like **Dave Maddison**, p. 88.

allowing patients with melanoma like **Bob Ribbans** to live with no evidence of disease, p. 94.

putting patients with multiple myeloma like **Steve Herz** into remission, p. 92.

RESEARCH EXPANDS CANCER TREATMENT OPTIONS

Leading to new and expanded uses for molecularly targeted therapeutics, including:

the first inhibitor to target the most frequent cause of resistance to EGFR inhibitors, which is benefiting patients with lung cancer like **Ginger Tam**, p. 72.

a first-in-class BCL2 inhibitor, which is benefiting patients with chronic lymphocytic leukemia like **Brian Parkinson**, p. 76.

a new ALK inhibitor for treating patients with lung cancer.

CANCER IN 2016

In this section you will learn:

- In the United States, the overall cancer death rate is decreasing, and the number of cancer survivors is increasing.
- The reduction in the U.S. cancer death rate from 1991 to 2012 translates into 1.7 million cancer deaths avoided.
- In 2016, 595,690 people are expected to die from some form of cancer in the United States, making it the second most common cause of death.
- Not all segments of the U.S. population benefit equally from advances against cancer.
- The cost of cancer is enormous, both in the United States and globally.

13 of 40 (32%)

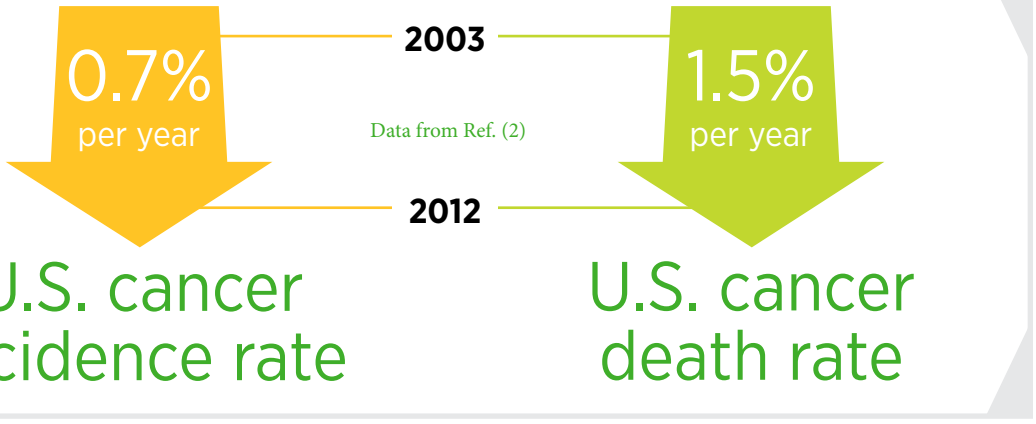
novel drugs approved by the FDA's Center for Drug Evaluation and Research from Aug. 1, 2015, to July 31, 2016, were for use in oncology.

RESEARCH: POWERING PROGRESS AGAINST CANCER

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

Each clinical and legislative advance against cancer is the culmination of many years of hard work by individuals from all segments of the biomedical research community (see sidebar on **The Biomedical Research Community: Powering Progress Together**, p. 9).

Among the most prominent clinical advances against cancer are the new medical products approved for use by the U.S. Food and Drug Administration (FDA). Bringing a new medical product from initial research discovery



THE BIOMEDICAL RESEARCH COMMUNITY: POWERING PROGRESS TOGETHER

Progress against cancer occurs when individuals in different segments of the biomedical research community work together. Further increasing collaboration between 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;

policymakers;

regulators;

philanthropic organizations and cancer-focused foundations;

federal funding organizations; and

payers.

Adapted from (1)

through development, approval by regulatory agencies, and then into the clinic is a complex, multifaceted process (see **Biomedical Research**, p. 48). From Aug. 1, 2015, to July 31, 2016, the FDA approved 18 new medical products for use in oncology—13 new anticancer therapeutics, one new cancer screening test, one new diagnostic test, two new diagnostic imaging agents, and a new medical device (see **Table 1**, p. 10). During this period, the FDA also approved new uses for 11 previously approved anticancer therapeutics.

Clinical advances such as those listed in **Table 1** (see p. 10) are helping drive down U.S. cancer incidence and death rates and increase the number of children and adults who survive a cancer diagnosis (see **Table 2**, p.12, for data on childhood cancer) (2-5). In fact, the age-adjusted U.S. cancer death rate declined by 23 percent from 1991 to 2012, a reduction that translates into 1.7 million cancer deaths avoided (3). 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 2011 (3).

TABLE 1 FDA-APPROVED MEDICAL PRODUCTS FOR THE TREATMENT OF CANCER: AUG. 1, 2015–JULY 31, 2016

Approved Indication	Generic Name	Trade Name	Formulation
Angiogenesis Inhibitors			
Certain form of kidney cancer†	cabozantinib	Cabometyx	
Certain form of kidney cancer†	lenvatinib	Lenvima	
Cell-signaling Inhibitors			
Certain form of lung cancer†	afatinib	Gilotrif	
Certain form of lung cancer	alectinib	Alecensa	
Certain form of melanoma	cobimetinib AND vemurafenib†*	Cotellic AND Zelboraf	
Certain form of lung cancer†	crizotinib	Xalkori	
Certain neuroendocrine tumors†	everolimus	Afinitor	
Certain form of lung cancer	necitumumab	Portrazza	
Certain form of lung cancer	osimertinib*	Tagrisso	
Cell-cytoskeleton Modifying Agents			
Liposarcoma†	eribulin mesylate	Halaven	
Cell-death Promoting Agents			
Certain form of leukemia	venetoclax	Venclexta	
DNA-damaging Agents			
Colorectal cancer	trifluridine AND tipiracil	Lonsurf	
Pancreatic cancer	irinotecan liposome injection	Onivyde	
Gene-transcription Modifiers			
Liposarcoma and leiomyosarcoma	trabectedin	Yondelis	
Immunotherapeutics			
Multiple myeloma	daratumumab	Darzalex	
Multiple myeloma	elotuzumab	Empliciti	
Melanoma	ipilimumab AND† nivolumab	Yervoy AND Opdivo	
Certain types of lung† and kidney† cancers and certain type of lymphoma†	nivolumab	Opdivo	
Certain type of lymphoma†	obinutuzumab	Gazyva	
Certain type of lung cancer†	pembrolizumab*	Keytruda	
Melanoma	talimogene laherparepvec^	Imlygic	
Certain type of bladder cancer	atezolizumab	Tecentriq	
Proteasome Inhibitors			
Multiple myeloma	ixazomib	Ninlaro	
Cancer Screening Tests			
Colorectal cancer	system, colorectal neoplasia, DNA methylation and hemoglobin detection test	Epi proColon	
Imaging Agents			
Certain neuroendocrine tumors	gallium (Ga) 68 DOTATATE	Netspot	
Prostate cancer	fluciclovine fluorine (F) 18	Axumin	
Companion Diagnostic Tests			
Certain type of lung cancer		cobas EGFR Mutation Test v2	

^first in class. †new use for 2015–2016. *requires a companion diagnostic

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

The research that powers the significant advances that have been and continue to be made against cancer is made possible by investments from governments, philanthropic individuals and organizations, and the private sector the world over. Of particular importance in the United States are federal investments in biomedical research and government agencies conducting research such as the FDA and the Centers for Disease Control and Prevention (CDC). 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 tremendous progress against cancer, this collection of diseases continues to be an enormous public health challenge worldwide, accounting for one in every seven deaths that occur around the world (6) (see **Figure 1**). In the United States alone, it is predicted that 595,690 people will die from some form of cancer in 2016, making it the second most common cause of death after heart disease (3).

By 2013, cancer had overtaken cardiovascular disease as the leading cause of death in

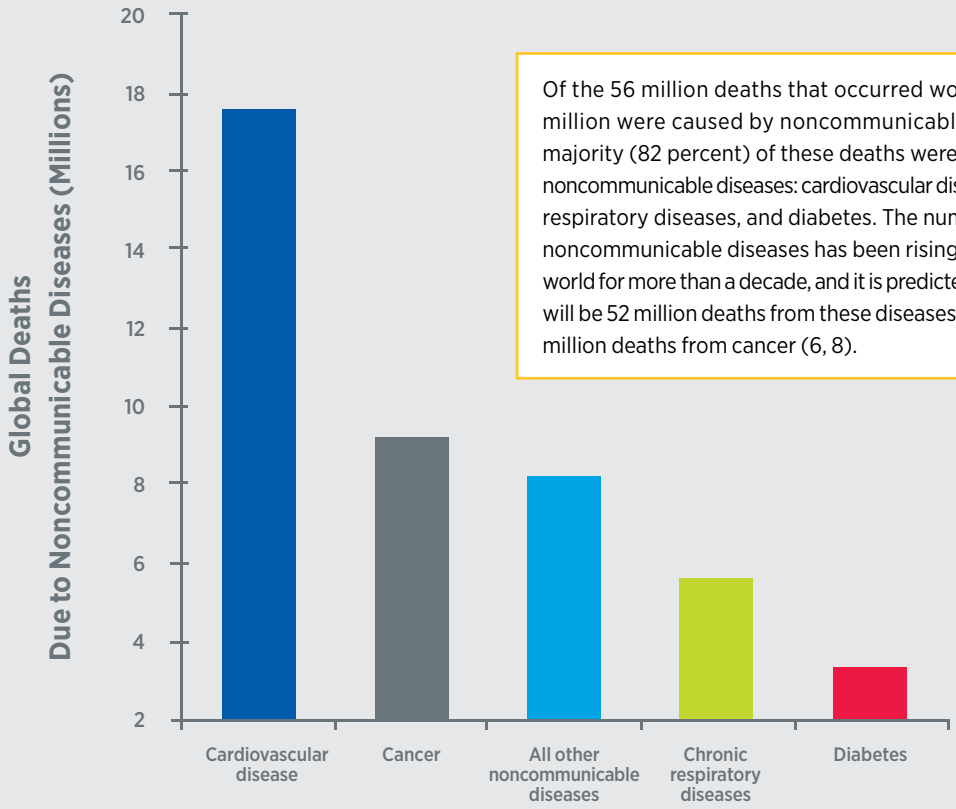
23

U.S. states (7).

One of the challenges we face is that advances have not been uniform for all forms of cancer (see **Table 3**, p. 14). For example, while the incidence 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 kidney, liver, and pancreatic cancer, as well as melanoma and childhood cancer—have been increasing (2). Overall 5-year relative survival rates for U.S. patients also vary widely depending on the form of cancer diagnosed (3). Overall 5-year relative survival rates for women with invasive breast cancer and men with

FIGURE 1

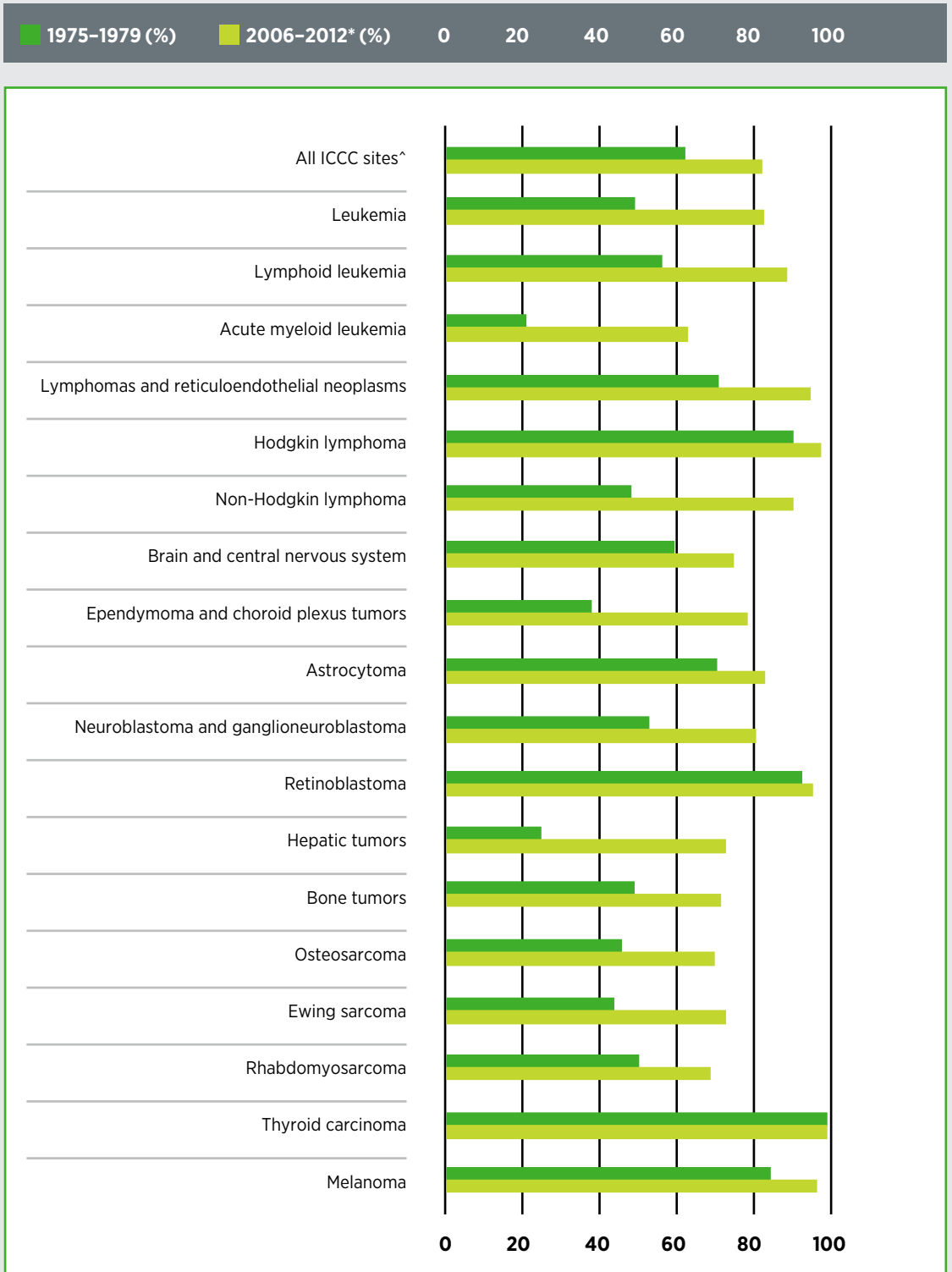
CANCER: A GLOBAL CHALLENGE



Of the 56 million deaths that occurred worldwide in 2012, 38 million were caused by noncommunicable diseases (6). The majority (82 percent) of these deaths were caused by just four noncommunicable diseases: cardiovascular disease, cancer, chronic respiratory diseases, and diabetes. The number of deaths from noncommunicable diseases has been rising in every part of the world for more than a decade, and it is predicted that globally, there will be 52 million deaths from these diseases in 2030 including 13 million deaths from cancer (6, 8).

TABLE 2

COMPARISON OF RELATIVE 5-YEAR SURVIVAL RATES FOR CHILDHOOD CANCERS (0-19 YRS) BETWEEN 1975-79 AND 2006-2012



*Followed into 2012

^Cancers in children and younger adolescents are classified by histology (tissue type) using the International Classification of Childhood Cancers (ICCC)

Data from Ref. (5) and Ref. (10)

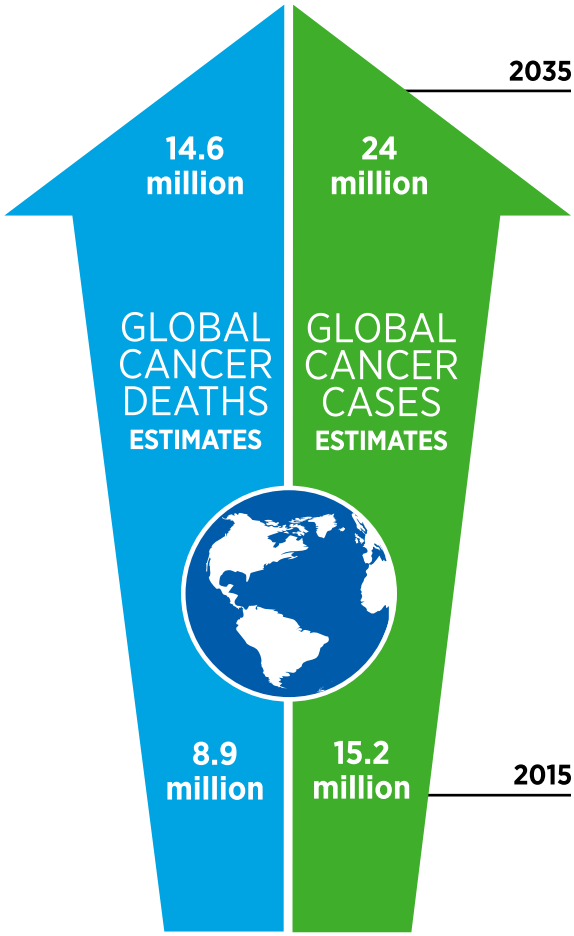
prostate cancer are 89 percent and 99 percent, respectively, while those for U.S. adults with liver or pancreatic cancer are just 17 percent and 7 percent, respectively (3).

Another challenge is that advances have not been uniform for all patients diagnosed with a given form of cancer. Five-year relative survival rates vary with stage at diagnosis and among different segments of the population (see sidebar on **What Are Cancer Health Disparities?**, p. 15 and the sidebar on **U.S. Cancer Health Disparities**, p. 16).

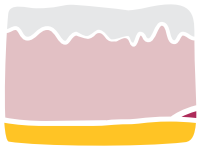
Of concern is the fact that the devastating toll of cancer is predicted to increase significantly unless more effective strategies for cancer prevention, early detection, and treatment are developed. This is largely because cancer is primarily a disease of aging (9), and the segment of the world population age 65 and older is expected to almost double by 2035, rising from 616 million in 2015 to 1.157 billion in 2035 (15). During this period, the number of global cancer cases is anticipated to increase dramatically, reaching 24 million in 2035 (8). Also contributing to the projected increase in the number of cancer cases are high rates of tobacco use, obesity, infection, and physical inactivity, which are linked to some common types of cancer (6).

55%
of U.S. cancer diagnoses occur among those age 65 or older (9).

The United States is not immune to the rising burden of cancer (see sidebar on **The Growing Public Health Challenge of Cancer in the United States**, p. 17). Thus, it is imperative that we work with the global biomedical research community to address cancer incidence and mortality and power more progress against cancer.



Stage at diagnosis can affect 5-year relative survival (9):



Melanoma:

92%	98%	63%	17%
overall	local	regional	distant

Kidney and renal pelvis cancer:

74%	93%	66%	12%
overall	local	regional	distant

TABLE 3 ESTIMATED INCIDENCE AND MORTALITY FOR SELECT CANCERS*

	ESTIMATED 2016 INCIDENCE			ESTIMATED 2016 DEATHS		
	Total	Male	Female	Total	Male	Female
All Sites	**1,685,210**	**841,390**	**843,820**	**595,690**	**314,290**	**281,400**
Head and Neck Region						
Brain & other nervous system	23,770	13,350	10,420	16,050	9,440	6,610
Eye & orbit	2,810	1,510	1,300	280	150	130
Oral cavity & pharynx	48,330	34,780	13,550	9,570	6,910	2,660
Tongue	16,100	11,700	4,400	2,290	1,570	720
Mouth	12,910	7,600	5,310	2,520	1,630	890
Pharynx	16,420	13,350	3,070	3,080	2,400	680
Larynx	13,430	10,550	2,880	3,620	2,890	730
Lung & bronchus	224,390	117,920	106,470	158,080	85,920	72,160
Breast	249,260	2,600	246,660	40,890	440	40,450
Gastrointestinal (GI) System						
Esophagus	16,910	13,460	3,450	15,690	12,720	2,970
Stomach	26,370	16,480	9,890	10,730	6,540	4,190
Liver & intrahepatic bile duct	39,230	28,410	10,820	27,170	18,280	8,890
Gallbladder & other biliary	11,420	5,270	6,150	3,710	1,630	2,080
Pancreas	53,070	27,670	25,400	41,780	21,450	20,330
Small intestine	10,090	5,390	4,700	1,330	710	620
Colon and rectum†	95,270	47,710	47,560	49,190	26,020	23,170
Anus, anal canal, & anorectum	8,080	2,920	5,160	1,080	440	640
Urogenital System						
Kidney & renal pelvis	62,700	39,650	23,050	14,240	9,240	5,000
Ovary	22,280		22,280	14,240		14,240
Uterine corpus	60,050		60,050	10,470		10,470
Uterine cervix	12,990		12,990	4,120		4,120
Urinary bladder	76,960	58,950	18,010	16,390	11,820	4,570
Prostate	180,890	180,890		26,120	26,120	
Testis	8,720	8,720		380	380	
Skin						
Skin (excluding basal & squamous)	83,510	51,650	31,860	13,650	9,330	4,320
Melanoma-skin	76,380	46,870	29,510	10,130	6,750	3,380
Hematological System						
Leukemia	60,140	34,090	26,050	24,400	14,130	10,270
Acute lymphocytic leukemia	6,590	3,590	3,000	1,430	800	630
Chronic lymphocytic leukemia	18,960	10,830	8,130	4,660	2,880	1,780
Acute myeloid leukemia	19,950	11,130	8,820	10,430	5,950	4,480
Chronic myeloid leukemia	8,220	4,610	3,610	1,070	570	500
Lymphoma	81,080	44,960	36,120	21,270	12,160	9,110
Hodgkin lymphoma	8,500	4,790	3,710	1,120	640	480
Non-Hodgkin lymphoma	72,580	40,170	32,410	20,150	11,520	8,630
Myeloma	30,330	17,900	12,430	12,650	6,430	6,220
Other Cancers						
Bones & joints	3,300	1,850	1,450	1,490	860	630
Soft tissue (including heart)	12,310	6,980	5,330	4,990	2,680	2,310

*Rounded to the nearest 10; estimated new cases exclude basal cell and squamous cell skin cancers and in situ carcinomas except urinary bladder. About 61,000 cases of carcinoma in situ of the female breast and 68,480 melanoma in situ will be newly diagnosed in 2016. †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 1995-2012 as reported by the North American Association of Central Cancer Registries (NAACCR), represesnting about 98% of the U.S. population. Estimated deaths are based on U.S. mortality data during 1997-2012, National Center for Health Statistics, Centers for Disease Control and Prevention.

WHAT ARE CANCER HEALTH DISPARITIES?

According to the National Cancer Institute, cancer health disparities in the United States are defined as differences that should not exist in cancer incidence, prevalence, death, survivorship, and burden of cancer among certain segments of the U.S. population, including:

racial and ethnic minority groups;

individuals who lack or have limited access to health care;

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

refugees or asylum seekers;

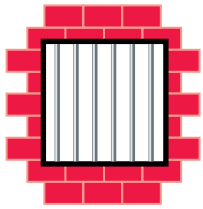
individuals with disabilities;

individuals of low socioeconomic status;

residents in certain geographic locations, including rural areas;

immigrants;

individuals who are incarcerated; and



the elderly.

WHY DO THEY EXIST?

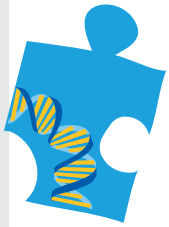
Complex and interrelated factors contribute to U.S. cancer health disparities. The factors may include, but are not limited to, differences or inequalities in:

access to and use of health care;

treatments received;

exposure to environmental cancer risk factors;

genetics;



social and economic status;

cultural beliefs; and

health literacy.

The interrelated nature of many of these factors makes it difficult to isolate and study the relative contribution of each. 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. Only with new insights will we develop and implement interventions that will eliminate cancer for all.

Adapted from (1)

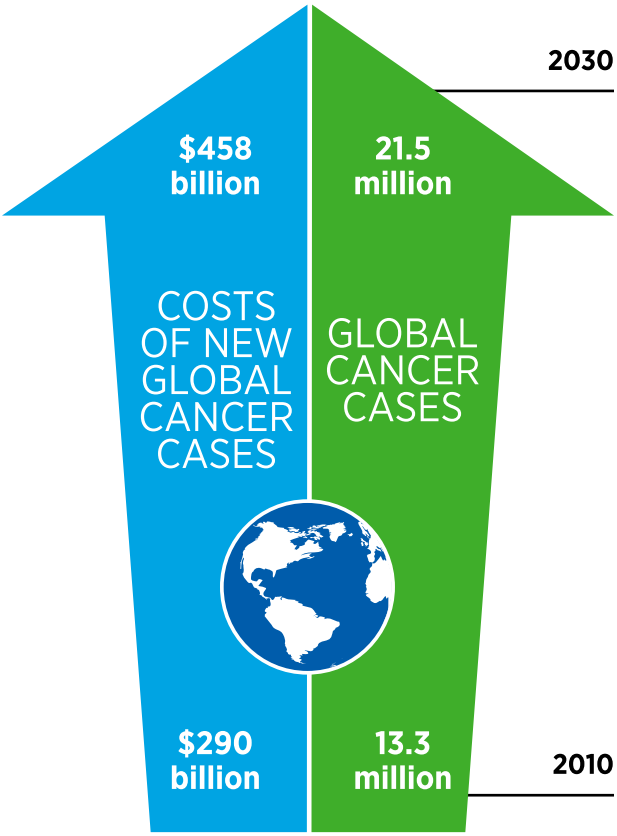
U.S. CANCER HEALTH DISPARITIES

Great strides have been made in cancer prevention, detection, diagnosis, treatment, and, in certain cases, cure. However, not all segments of the U.S. population have benefited equally from these advances (see sidebar on What Are Cancer Health Disparities?, p. 15). As a result, differences that should not exist in cancer incidence, prevalence, death, survivorship, and burden of cancer exist among certain segments of the U.S. population. Some examples of cancer health disparities are highlighted here:

27% HIGHER	The overall cancer death rate among black men is 27 percent higher than among white men (2).
14% HIGHER	The overall cancer death rate among black women is 14 percent higher than among white women (2).
MORE THAN **DOUBLE**	Prostate cancer death rates among black men are more than double those for any other racial or ethnic group (3).
23% MORE LIKELY	Hispanic children are 23 percent more likely to develop leukemia than non-Hispanic children (10).
2X	Asians and Pacific Islanders are about twice as likely to develop and die from liver cancer as their white counterparts (2).
62% MORE LIKELY	American Indian/Alaska Native women are 62 percent more likely to develop kidney cancer than white women, and 80 percent more likely to die from the disease (2).
	Colorectal cancer death rates in the lower Mississippi Delta, west central Appalachia, and eastern Virginia/North Carolina are elevated compared with the rest of the United States (11).
32% LESS LIKELY	Advanced-stage ovarian cancer patients of low socioeconomic status are 32 percent less likely to receive standard overall care compared with those of high socioeconomic status (12).
	Lesbian women are less likely to undergo screening for breast and cervical cancer compared with heterosexual women (13, 14); however, more research is needed to determine whether this finding translates into a disparity in cancer incidence.

CANCER: A COSTLY DISEASE. RESEARCH: A VITAL INVESTMENT

Cancer exerts an immense global toll that is felt not only through the number of lives it affects each year, but also through its significant economic impact. With the number of cancer cases projected to increase substantially in the next few decades, it is anticipated that the economic burden will rise, too. One study estimates that the global cost of new cancer cases will increase from $290 billion in 2010 to $458 billion in 2030 (21).

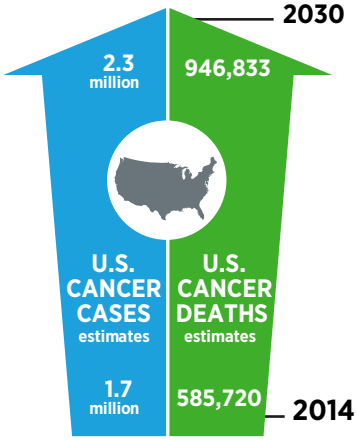


Data from (21)

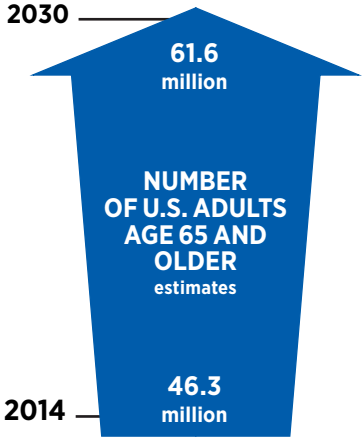
In the United States, the direct medical costs of cancer care are projected to rise from nearly $125 billion in 2010 to $156 billion in 2020. These costs stand in stark contrast to the NIH budget for fiscal year (FY) 2016, which is $32.31 billion, of which $5.21 billion is dedicated to the NCI.

The increasing personal and economic burden of cancer underscores the urgent need for more research so that we can accelerate the pace of progress against cancer. Recent advances, some of which are highlighted in this report, were made as a direct result of the cumulative efforts of researchers from across the spectrum of research disciplines. Much of their work, as well as the federal regulatory agency that ensures the safety and efficacy of medical device and therapeutic advances—the FDA—is supported by funds from the federal government. Although the $2 billion increase to the NIH budget in FY 2016 was a welcome boost, it is imperative that Congress and the Administration 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.

THE GROWING PUBLIC HEALTH CHALLENGE OF CANCER IN THE UNITED STATES



Cancer is a leading cause of morbidity and mortality in the United States (16, 17). It is expected that the public health challenge it poses will grow considerably in the coming decades if more effective strategies for cancer prevention, early detection, and treatment are not developed (8, 18).



This growing challenge will be fueled by an increase in the number of U.S. adults age 65 and older (19), continued use of cigarettes by 15 percent of U.S. adults (20), and high rates of obesity and physical inactivity (17).

DEVELOPING CANCER

In this section you will learn:

- Cancer is not one disease; it is a collection of diseases characterized by the uncontrolled growth of cells.
- Many cancers are progressive in nature, providing distinct points for medical intervention to prevent cancer, detect it early, or treat progressive disease.
- The most advanced stage of cancer, metastatic disease, accounts for most cancer-related deaths.
- 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 more we know about the interplay among the individual factors influencing cancer biology, the more precisely we can prevent and treat cancer.

Research has taught us that cancer is a complex disease. In fact, it is not just one disease but rather a collection of many diseases that arise when the processes that control the multiplication and life span of normal cells go awry.

In adults, cell multiplication is a very tightly controlled process that occurs primarily only to replace cells that die due to exposure to various external factors or as a result of normal wear and tear.

If the processes that control the multiplication and life span of normal cells go awry, the cells start multiplying uncontrollably, fail to die when they should, and begin to accumulate. In body organs and tissues, the accumulating cells form a tumor mass, whereas in the blood or bone marrow, they crowd out the normal cells. Over time, some cancer cells within the tumor mass gain the ability to invade local tissues. Some also gain the ability to spread (or metastasize) to distant sites.

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.

Changes, or mutations, in the genetic material of a normal cell are the primary cause of cancer initiation. Over time, additional mutations are acquired by cells within a growing tumor mass, and this drives cancer progression. 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 may have different genetic changes. In general, the more genetically heterogeneous a tumor is, the harder it is to effectively treat.

Not all mutations acquired by a cell contribute to cancer initiation and development. In fact, 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. Numerous interrelated factors influence mutation acquisition and determine the overall risk that a person will develop a particular type of cancer (see sidebar on **Why Did I Get This Cancer?** p. 19).

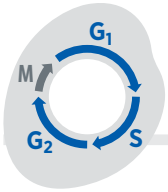
CANCER DEVELOPMENT: INFLUENCES INSIDE THE CELL

The accumulation of mutations in the genetic material of a cell over time is the predominant cause of cancer initiation and progression (see sidebar on **Genetic and Epigenetic Control of Cell Function**, p. 20). A genetic mutation is a change in the type or order of the four deoxyribonucleic acid (DNA) units, called bases, that make up the genetic

WHY DID I GET THIS CANCER?

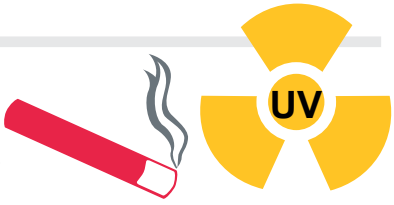
Cancer initiation and progression are predominantly caused by the accumulation of changes, or mutations, in the genetic material of a cell over time. Some genetic mutations are inherited from your parents and are present in each cell of the body from birth but most genetic mutations are acquired during your lifetime.

Five to 10 percent of all new U.S. cancer cases are linked to inherited genetic mutations (22).



Some mutations are acquired during cell multiplication, and the number of times a cell multiplies increases the chance it will acquire a mutation.

Some mutations are acquired as a result of exposure to factors that damage genetic material, such as toxins in tobacco smoke and ultraviolet (UV) light from the sun.

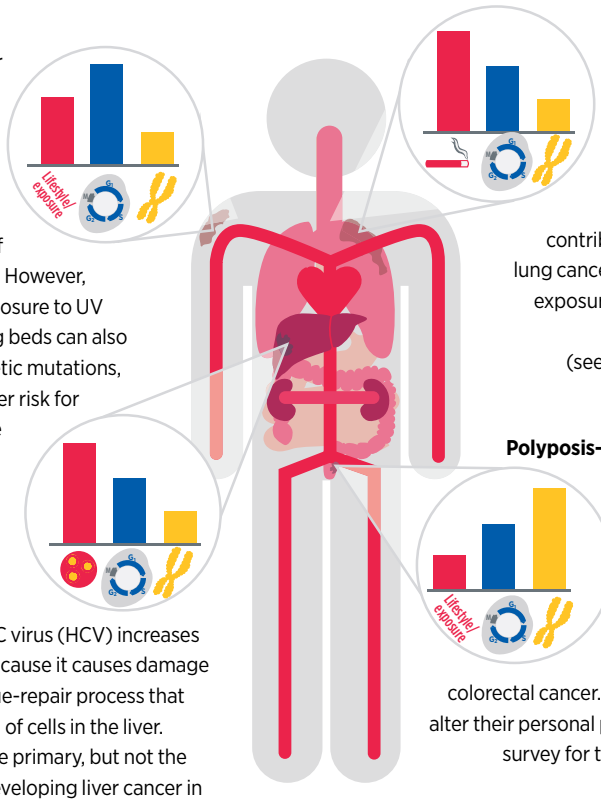


These factors come together to determine the chance that an individual cell has of acquiring mutations over time. This, in turn, helps determine the overall risk that a person will develop a particular type of cancer.

Simplified estimates of the relative contribution of each of the various sources of mutations to developing particular types of cancer are illustrated based on a recent study (23). This understanding can influence approaches for prevention and early detection of these and other types of cancer. Because cancer is caused by the accumulation of mutations over time, the older a person gets, the more likely he or she is to have a cell that has acquired a combination of genetic mutations causing it to become cancerous.

Basal Cell Carcinoma
Basal cells in the outermost layer of the skin are constantly multiplying to replace skin damaged by normal wear and tear. Thus, the number of cell multiplications is the primary contributor to the risk of developing basal cell carcinoma. However, it is not the only contributor. Exposure to UV radiation from the sun or tanning beds can also cause basal cells to acquire genetic mutations, and a person can reduce his or her risk for this cancer by adopting sun-safe habits and avoiding UV tanning devices (see **Protect Skin From UV Exposure**, p. 32).

Hepatitis C Virus–dependent Liver Cancer
Chronic infection with hepatitis C virus (HCV) increases a person's risk for liver cancer because it causes damage to the liver, which triggers a tissue-repair process that involves extensive multiplication of cells in the liver. Thus, chronic HCV infection is the primary, but not the only, contributor to the risk of developing liver cancer in infected individuals. HCV infection is treatable and preventable (see **Prevent Infection With Cancer-causing Pathogens**, p. 33).



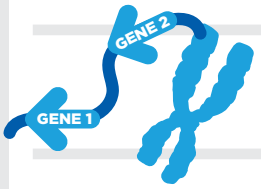
Smoking-dependent Lung Cancer
Acquired genetic mutations related to exposure to the toxins in cigarette smoke are the primary, but not the only, contributors to the risk of developing lung cancer. Eliminating tobacco use and exposure to smoke can prevent cancer from developing (see **Eliminate Tobacco Use**, p.24).

Familial Adenomatous Polyposis–dependent Colorectal Cancer
For individuals who inherit a mutation in the adenomatous polyposis coli (APC) gene, the inherited genetic mutation is the primary, but not the only, contributor to their risk of developing colorectal cancer. Such individuals, however, can alter their personal prevention plans to proactively survey for the earliest signs of disease and intervene as appropriate (see **Finding Cancer**, p. 38).

Adapted from (24)

GENETIC AND EPIGENETIC CONTROL OF CELL FUNCTION

Strings of four **deoxyribonucleic acid (DNA)** units called bases comprise the genetic material of a cell.



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**.

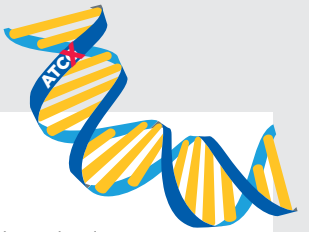
Special chemical marks, called **epigenetic marks**, on the DNA and histones together determine whether a gene is accessible for reading. The sum of these chemical marks across the entire genome is called the **epigenome**.

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

Adapted from (1)

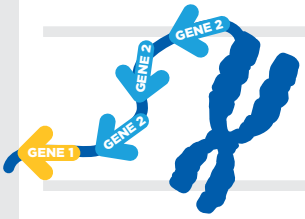
GENETIC MUTATIONS

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

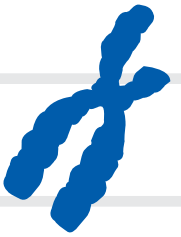


Single base changes

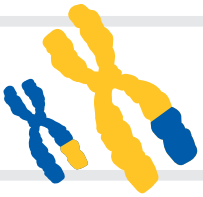
- Some mutations can lead to the generation of altered versions of normal proteins, and these may cause cancer to develop.
- Deletion or insertion of a single base can result in new proteins or loss of protein function, which can lead to cancer.



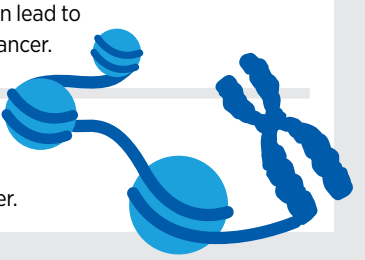
Extra copies of genes (gene amplification)
Higher quantities of certain proteins can result in enhanced cell survival and growth, leading to cancer.



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)

material of a cell. The order, or sequence, of DNA bases is a key determinant of what proteins are produced by a cell and how much of each protein is produced. Many different types of mutation contribute to cancer initiation and development, primarily by altering the amount or function of certain proteins (see sidebar on **Genetic Mutations**, p. 20).

In addition to genetic mutations, most cancer cells also have profound epigenetic abnormalities, compared with normal cells of the same tissue. In many cases, epigenetic alterations and genetic mutations work together to promote cancer development. Although genetic mutations are permanent, some epigenetic abnormalities appear to be reversible, and harnessing this discovery for therapeutic purposes is an area of intensive investigation.

CANCER DEVELOPMENT: INFLUENCES OUTSIDE THE CELL

Genetic mutations that disrupt the orderly processes controlling the multiplication and life span of normal cells are the main cause of cancer initiation and development. However, interactions between cancer cells and their environment—known as the tumor microenvironment—as well as interactions with systemic factors, also have an important role in cancer development (see sidebar on **Cancer Growth: Local and Global Influences**). In fact, cancer cells often exploit tumor microenvironment components to promote their multiplication and survival.

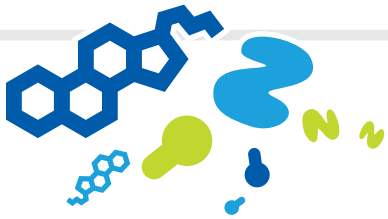
CANCER GROWTH: LOCAL AND GLOBAL INFLUENCES

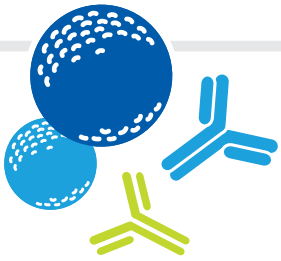
Solid tumors are much more complex than an isolated mass of proliferating cancer cells because cancer initiation, development, and progression are strongly influenced by interactions among cancer cells and numerous factors in their environment. Among the components of the tumor microenvironment are normal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

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

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).

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. In some situations of chronic inflammation, however, the immune system can promote cancer development and progression.

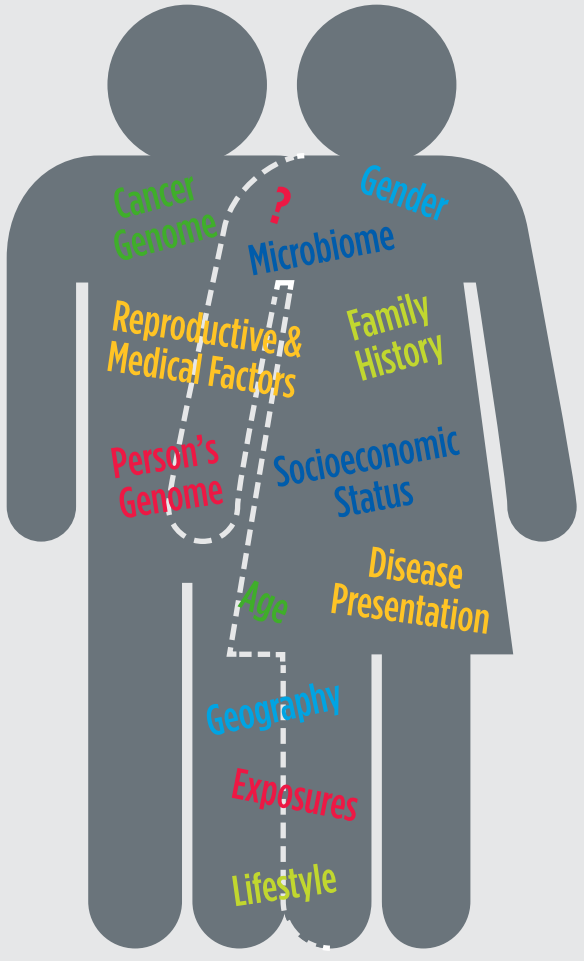
Adapted from (1)

CANCER DEVELOPMENT: A WHOLE-PATIENT PICTURE

Research has powered an explosion in our understanding of the individual factors inside and outside a cell that cause cancer initiation, development, and progression. It is also beginning to provide us with a picture of how these factors work together and are influenced by each person's unique biological characteristics. This knowledge is the essence of precision medicine, as well as the more nascent strategy of precision prevention (see **Figure 2**).

Precision prevention and medicine aim 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 those prevention interventions and/or treatments that are unlikely to be of benefit (25, 26). As we develop an even more comprehensive, whole-patient understanding of the way in which cancer starts, progresses, and results in sickness, we can expect to see an acceleration in the pace of progress in precision medicine and prevention for cancer (see **Anticipating Future Progress**, p. 100).

FIGURE 2 PRECISION MEDICINE AND PREVENTION



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. Factors such as a person's genome, the genome of his or her cancer, disease presentation, gender, exposures, lifestyle, microbiome, and other yet-to-be-discovered features (indicated by the question mark) are considered in precision medicine (25). Precision prevention is a conceptual framework that aims to tailor cancer prevention to the individual patient by accounting for the various factors that may play a role in developing a particular cancer (26); it is analogous to the manner in which precision medicine treats patients. The following factors could be considered in the implementation of precision prevention: a person's genome; age; gender; family history, including genetic predisposition to developing cancer (see **Table 5**, p. 43); lifestyle factors including tobacco and alcohol use, being overweight or obese, and levels of exercise; reproductive and medical factors; exposures to known carcinogens like viruses; socioeconomic status; and geography, as well as yet-to-be identified factors (indicated by the question mark). The order in which the factors appear in the images is not meant to imply that one factor is more important than another.

PREVENTING CANCER

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.
- Exposure to environmental cancer risk factors remains a challenge for certain segments of the U.S. population.

Factors that increase the chance of developing cancer are referred to as cancer risk factors. These factors directly or indirectly increase the chance that a cell will acquire a genetic mutation and therefore increase the chance that a cell will become cancerous (see sidebar on **Why Did I Get This Cancer?**, p. 19). Decades of research have led to the identification of numerous cancer risk factors (see **Figure 3**, p. 24) (27).

Many of the risk factors that have the biggest impact on cancer incidence are avoidable (see **Figure 3**, p. 24). For example, many cases of cancer could be prevented either by individuals modifying their behaviors or through the development and implementation of new public education and policy initiatives that encourage individuals to avoid cancer risk factors or protect people from cancer risk factors in the workplace or environment. In fact, a recent study suggests that between 40 percent and 60 percent of cancer cases among white Americans could be prevented if each person did not smoke, limited alcohol consumption, maintained a healthy weight, and undertook regular physical activity (29). These lifestyle behaviors also increase risk for cancer in other U.S. racial and ethnic groups, but the absolute contributions of these factors to cancer risk in nonwhite populations remain to be determined.

50%
of all global cancer cases are preventable (30).

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, major public education and policy initiatives to combat cigarette smoking have been credited with preventing almost 800,000 deaths from lung cancer from 1975 to 2000 (31). The researchers concluded, however, that this figure represented just 32 percent of the lung cancer deaths that could have been prevented during that period if tobacco control strategies had completely eliminated cigarette smoking (31).

Clearly, a great deal more research and more resources are needed to understand why some individuals continue to engage in risky behaviors despite current public education and policy initiatives, and how best to help these individuals eliminate or reduce their risk of some cancers. One recent

Through the Division of Cancer Prevention and Control, the

Centers for Disease Control and Prevention (CDC)

work with national cancer organizations, state health agencies, and other key groups to develop, implement, and promote effective strategies for preventing and controlling cancer.

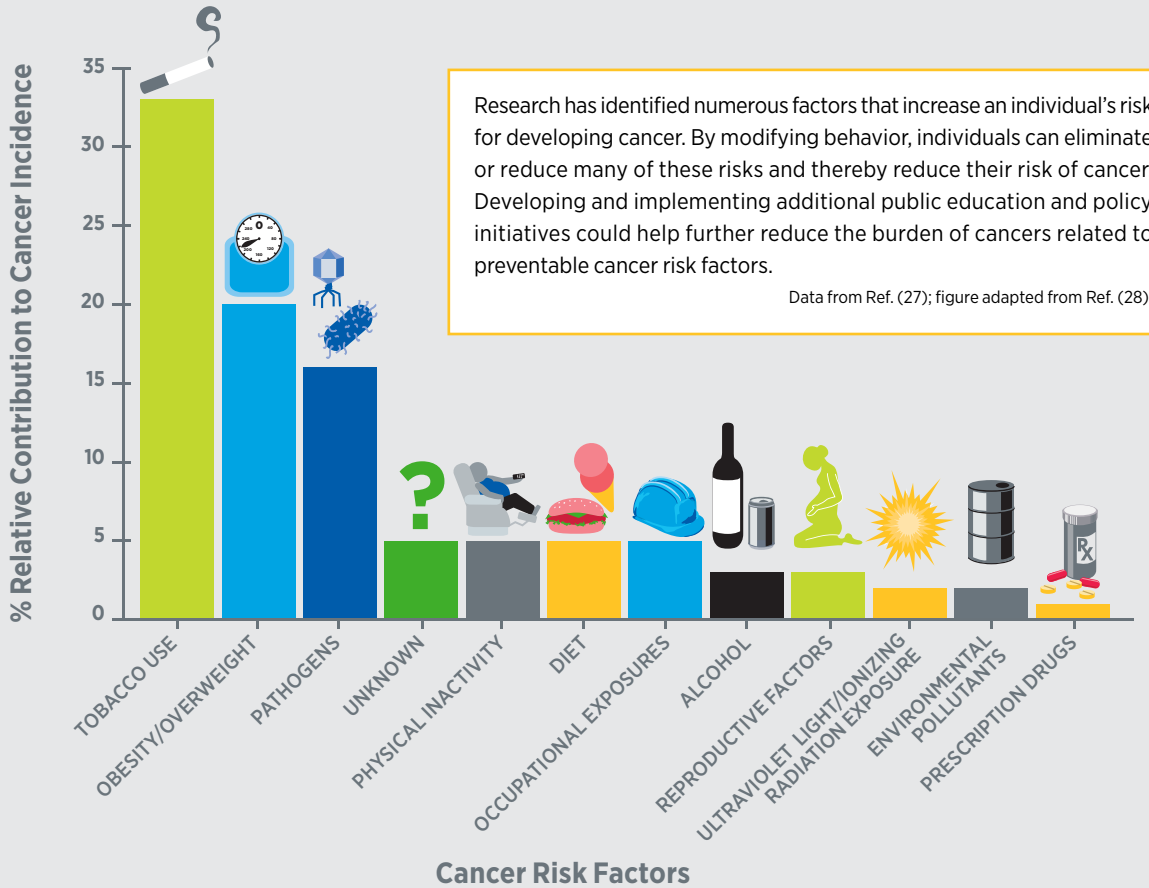
study suggested that the way that public education messages are framed can dramatically influence whether or not an individual modifies his or her behavior because it showed that dieting individuals who saw a message focusing on the negative aspects of unhealthy food actually increased their consumption of unhealthy foods (32).

ELIMINATE TOBACCO USE

Smoking tobacco exposes a person to toxicants that can cause genetic mutations, increasing his or her risk of developing not only lung cancer, but also 17 other types of cancer (see **Figure 4**, p. 25) (33). It is responsible for one in every three cases of cancer diagnosed in the United States each year (27). 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.

Since the relationship between tobacco use and cancer was first brought to the public's attention in 1964 (37), the

FIGURE 3 RISKY BUSINESS

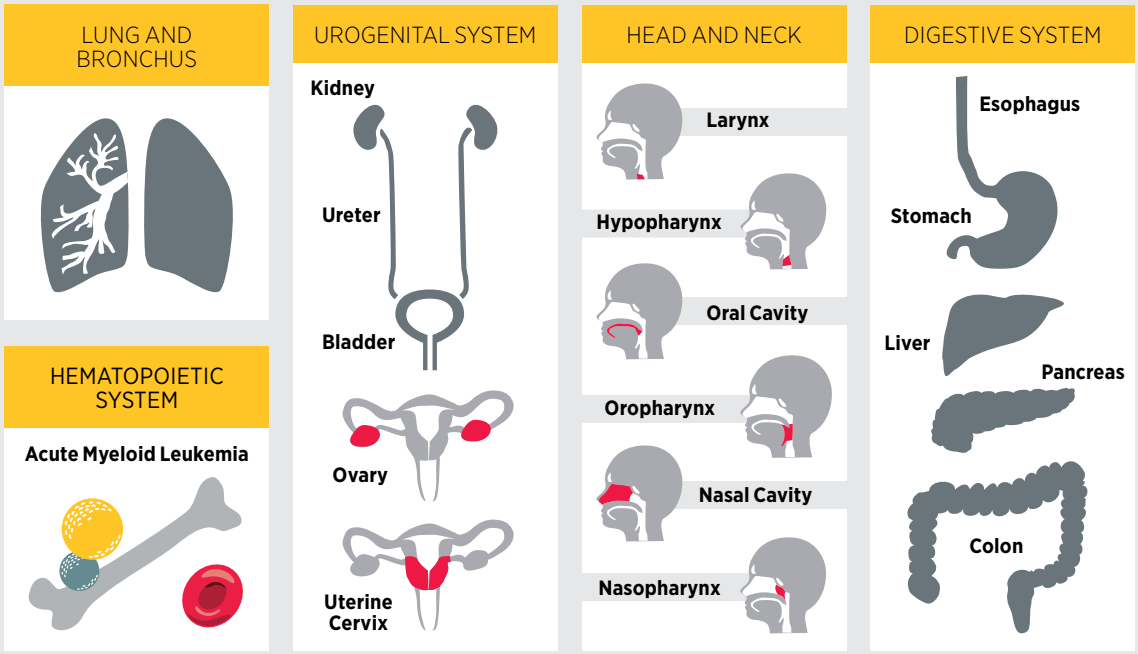


Research has identified numerous factors that increase an individual's risk for developing cancer. By modifying behavior, individuals can eliminate or reduce many of these risks and thereby reduce their risk of cancer. Developing and implementing additional public education and policy initiatives could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

Data from Ref. (27); figure adapted from Ref. (28).

FIGURE 4

BEYOND THE LUNGS: CANCERS CAUSED BY SMOKING TOBACCO



Smoking tobacco increases an individual's risk of developing not only lung cancer, but also 17 other types of cancer (34). 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 (35).

Figure adapted from Ref. (1)

development and implementation of major public education and policy initiatives have driven down cigarette smoking rates among U.S. adults from 42 percent in 1965 to 15 percent in 2015 (20, 34). In addition, the most recent data show declining use of cigarettes among high school students: In 2011, 15.8 percent of high school students were current users of cigarettes, compared with 9.3 percent in 2015 (38).

We have made tremendous progress reducing the public health burden of tobacco use, with researchers estimating that more than 8 million smoking-related deaths were prevented in the United States from 1964 to 2014 as a result of declines in cigarette smoking rates (39). The reductions in cigarette smoking rates have not been evenly distributed among all segments of the population, as defined by race, ethnicity, educational level, socioeconomic status, and place of residence (40). For example, 29.2 percent of non-Hispanic American Indians/Alaska Natives, 18.2 percent of non-Hispanic whites, 17.5 percent of non-Hispanic blacks, 11.2 percent of Hispanics, and 9.8 percent of non-Hispanic Asians are smokers (40).

In addition, U.S. adult use of other tobacco products that can cause certain types of cancer—cigars, smokeless

U.S. adults who smoke are

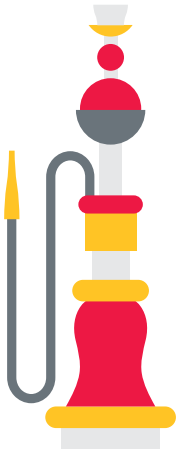
25 times

more likely to develop lung cancer than those who do not; but those who quit, cut their chance of dying from lung cancer in half within 10 years (35).

Quitting smoking abruptly is more likely to lead to lasting smoking cessation than cutting down gradually (36).

tobacco products (e.g., chewing tobacco and snuff), and pipe tobacco—has not changed over the past decade (41). Moreover, use of emerging tobacco products, such as electronic cigarettes (e-cigarettes) and water pipes, among high school students is increasing rapidly. In 2011, 1.5 percent of high school students were current users of e-cigarettes, and 4.1 percent were current users of hookahs, compared with 16.0 percent and 7.2 percent, respectively, in 2015 (38).

Given that 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 (43). In particular, we need to fully understand whether e-cigarettes have value as cigarette-smoking cessation aids and how they affect use of other tobacco products by smokers and nonsmokers (see sidebar on **E-cigarettes: What We Know and What We Need to Know**, p. 27) (44). We also need more research into the health consequences of smoking marijuana; for example, there is concern it could cause cancer because it involves the



Tar is the major source of tobacco carcinogens, and one water pipe tobacco smoking session delivers

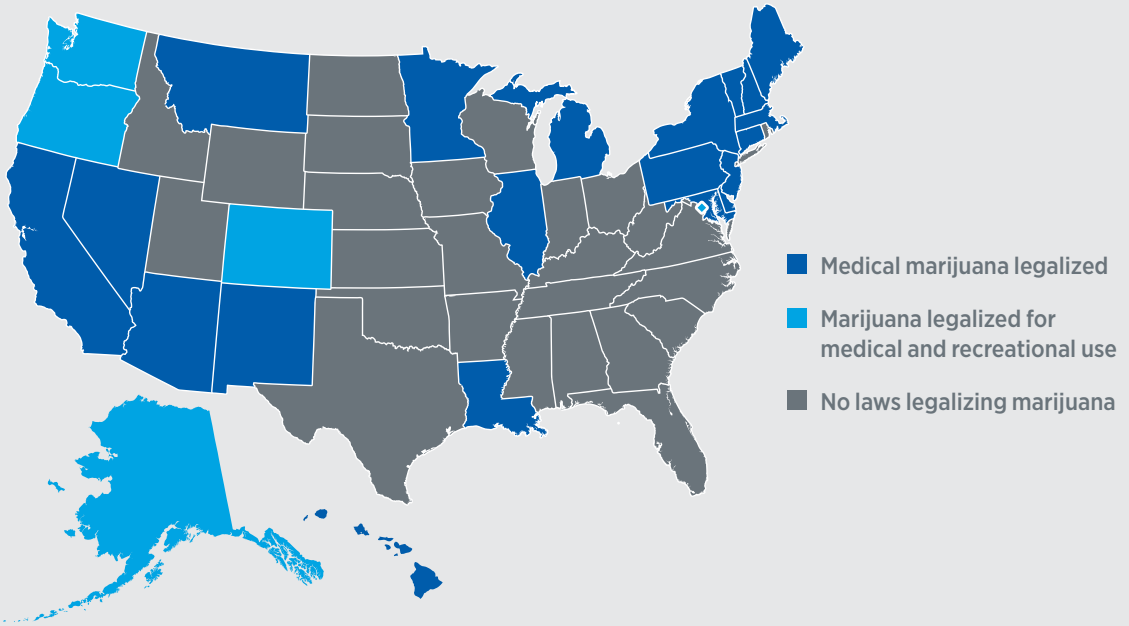
25 times the tar

of a single cigarette (42).

70%

of U.S. middle and high school students were exposed to e-cigarette advertisements in 2014 (46).

FIGURE 5 HIGH TIME TO LEARN MORE



There are laws legalizing some form of marijuana use in 25 U.S. states and the District of Columbia. In most states, marijuana is legalized only for medical purposes, but it is legalized for both medical and recreational purposes in Alaska, Colorado, Oregon, Washington, and the District of Columbia. With more and more states legalizing some form of marijuana use, it is imperative that we conduct more research to fully understand the health consequences of marijuana use, including how it affects cancer risk.

Data are current as of July 31, 2016, and are from Ref. (45)

E-CIGARETTES: WHAT WE KNOW AND WHAT WE NEED TO KNOW

WHAT WE KNOW

While conventional cigarettes deliver nicotine by combusting tobacco, electronic cigarettes (e-cigarettes) deliver nicotine by vaporizing a nicotine solution.

460+ BRANDS

More than 460 brands of e-cigarettes and other electronic nicotine delivery systems (ENDS) are available.

More than 7,700 flavors of nicotine solutions are available (44).

E-cigarette use among U.S. middle and high school students is rapidly increasing (38).

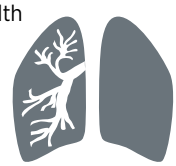
FDA APPROVED

In May 2016, the U.S. Food and Drug Administration announced it would begin regulating e-cigarettes, and banned the sale of these products to anyone under the age of 18.

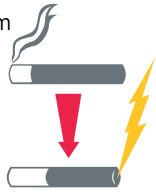
WHAT WE NEED TO KNOW (44)

ENDS and health

What are the health effects of acute and chronic ENDS use?



Does switching from cigarette smoking to ENDS use confer a health benefit?



Do different ENDS products vary in potential for addiction?

ENDS use

Who uses ENDS and why? Does this change over time?

Do flavorants affect the appeal and use of ENDS?

Does the marketing and availability of ENDS affect perception and use of ENDS?

Do tobacco-control policies affect the use of ENDS?

ENDS and cigarette smoking cessation

- Do ENDS aid cigarette smoking reduction and cessation?
- Can ENDS be used with current FDA-approved cessation medications?
- Should behavioral counseling be changed for ENDS cessation trials?
- Does short- or long-term ENDS use affect smoking relapse among those who have previously stopped using cigarettes?

ENDS products

- How do ENDS products differ from one other?
- Can ENDS product testing be standardized?

Adapted from (1)

burning of an organic material, much like tobacco smoking. The need for this research is driven by the growing number of states that have legalized marijuana use for medical and/or recreational purposes (see **Figure 5**, p. 26).

A number of new tobacco control policy initiatives have been recently announced in the United States, the most prominent of which 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**). In addition, a growing number of cities, counties, and states, most recently California, have passed legislation raising the minimum age of sale of tobacco products to 21 (47). This is important because nearly everyone who buys cigarettes for U.S. minors is under the age of 21 (47), and it has been predicted that if implemented nationwide, such legislation could lead to a 12 percent reduction in smoking prevalence (48).

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

Researchers estimate that one in every five new cases of cancer diagnosed in the United States is related to people being overweight or obese, being inactive, and/or eating a poor diet (49). Therefore, maintaining a healthy weight, being physically active, and consuming a balanced diet are effective ways a person can lower his or her risk of developing or dying from cancer (see sidebar on **Reduce Your Risk for Cancer Linked to Being Overweight or Obese, Being Inactive, and/or Consuming a Poor Diet**, p. 29).

ENHANCING TOBACCO CONTROL THROUGH FDA REGULATION

The U.S. Food and Drug Administration (FDA) has had the authority to regulate tobacco products since 2009. 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 through an amendment to the 2009 Family Smoking Prevention and Tobacco Control Act (Tobacco Control Act). The key provisions of this extended rule include:

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

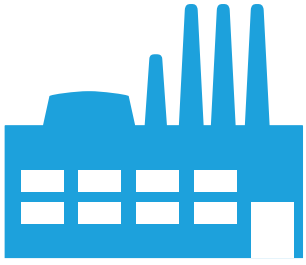
Requires a premarket review process and authorization of new tobacco products that reviews manufacturers' claims and requires the disclosure of ingredients and reporting of harmful or potentially harmful components.

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.

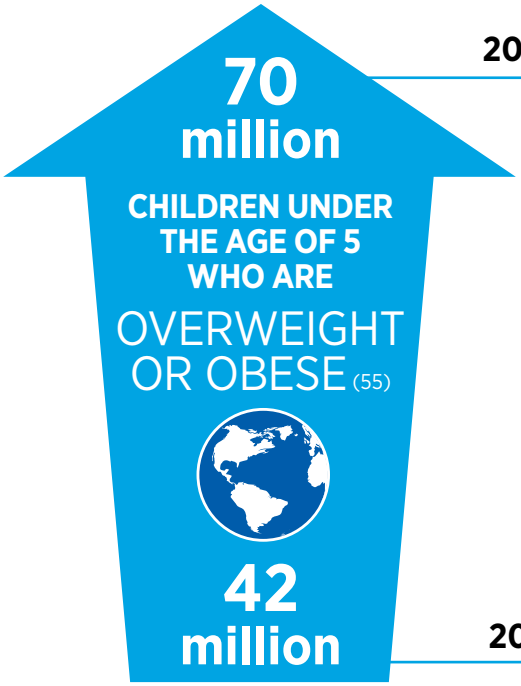
Prohibits the distribution of free samples.

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.



Being overweight or obese as an adult increases a person's risk for 14 types of cancer (see **Figure 6**, p. 30) (50), and it is estimated to have been responsible for about 481,000 of the new cases of adult cancer diagnosed worldwide in 2012 (51). Therefore, it is extremely concerning that in the United States, 71 percent of adults age 20 or over are overweight or obese (52), 32 percent of youth ages 2 to 19 are overweight or obese (52), and more than half of U.S. adults and 73 percent of high school students do not meet the relevant recommended guidelines for aerobic physical activity (see sidebar on **Physical Activity Guidelines**, p. 31) (20, 53).

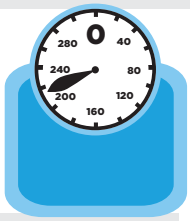


The importance of following guidelines for leisure time physical activity is highlighted by a recent study showing that increasing levels of leisure time aerobic physical activity decreased risk for developing 13 types of cancer (56). For 10 of these cancers, this held true regardless of body mass index (BMI), the most common measure of whether or not a person is underweight, normal weight, overweight, or obese.

Physical inactivity cost health care systems **$53.8 billion** worldwide in 2013 (54).

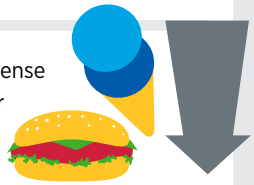
REDUCE YOUR RISK FOR CANCERS LINKED TO BEING OVERWEIGHT OR OBESE, BEING INACTIVE, AND/OR CONSUMING A POOR DIET

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:

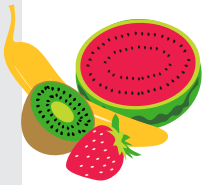


Be as lean as possible without becoming underweight, because 14 types of cancer have been causally linked to being obese or overweight (see **Figure 6**, p. 30).

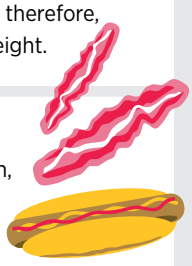
Be physically active for at least 30 minutes every day, because regular physical activity can decrease risk for certain cancers.



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.



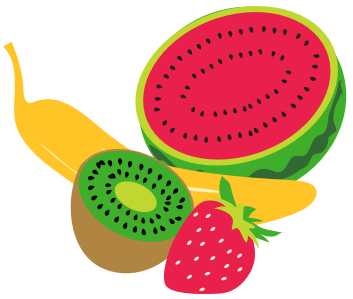
Eat more of a variety of vegetables, fruits, whole grains, and beans, because these foods have a low energy density and, therefore, promote healthy weight.



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:
http://www.wcrf.org/int/research-we-fund/our-cancer-prevention-recommendations
Adapted from (24)



From 2007 to 2010,

87%

of U.S. adults did not meet U.S. government recommendations for daily fruit intake and

76%

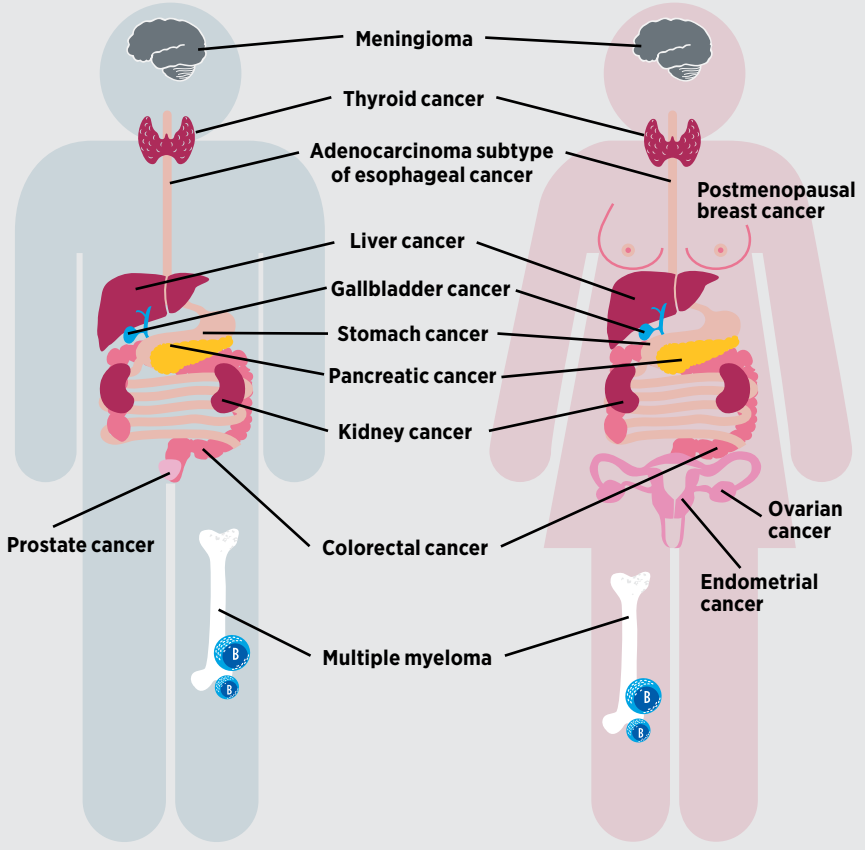
did not meet the recommendations for daily vegetable intake (61).

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 (57, 58). Nevertheless, concerted efforts by individuals, families, communities, schools, workplaces, institutions, health care professionals, media, industry, government, and multinational bodies are required to implement any strategy to promote the maintenance of a healthy weight and the participation in regular physical activity.

In addition, 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* (59). 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

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 (50, 204).

Figure adapted from Ref. (24)

on food packaging, including the new requirement for information about how much sugar has been added to the food product (60).

The new public education and policy initiatives are important steps toward reducing the burden of cancer caused by being overweight or obese, being inactive, and/or eating a poor diet. More research is needed, however, to better understand the effect on cancer risk of exposure to these cancer risk factors at various stages of life. For example, recent data suggest that increased body weight during childhood and adolescence may increase risk for colorectal cancer later in life (62, 63), while eating plenty of fruit during adolescence may decrease risk for breast cancer in later life (64), although more research is required to confirm these findings.

New U.S. dietary guidelines recommend added sugars account for no more than

10%

of daily calories, which is equivalent to about 50 grams of added sugar per day (59).

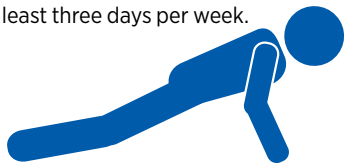
PHYSICAL ACTIVITY GUIDELINES

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 pushups at least three days per week.

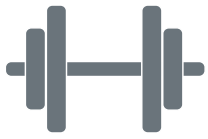


FOR ADULTS

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)

PROTECT SKIN FROM UV EXPOSURE

For most of the nearly 5 million patients with skin cancer who are treated each year in the United States, their disease was caused by genetic mutations arising as a result of exposure to ultraviolet (UV) light from the sun, sunlamps, tanning beds, and tanning booths (65). In fact, it is estimated that exposure to UV radiation, primarily from the sun, causes as many as 90 percent of U.S. cases of melanoma, the most deadly form of skin cancer. About 8 percent of cases are attributable to indoor tanning (66). 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**).

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 recommend that you:

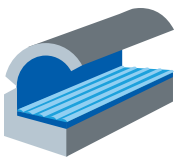
seek shade and limit time in the sun, especially around midday;

wear clothing that covers your arms and legs;

wear a wide-brimmed hat;

wear wrap-around sunglasses;

apply a sunscreen rated sun protection factor (SPF) 15 or higher at least every 2 hours and after swimming, sweating, and toweling off; and



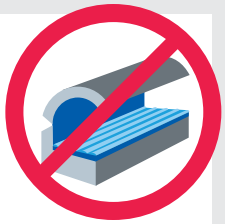
avoid indoor tanning with UV devices like sunlamps, sunbeds, and tanning booths.

Adapted from (24)

21,000 U.S. melanoma cases each year from 2020 to 2030 could be prevented by implementing a comprehensive skin cancer prevention program (71).

INDOOR TANNING LEGISLATION

Use of an indoor UV tanning device increases a person's risk for melanoma by 20 percent, and each additional use increases risk a further 1.8 percent (73). The U.S. Food and Drug Administration is considering proposals that would ban the use of indoor UV tanning devices by people younger than age 18 and require manufacturers and indoor tanning facilities to take more actions to improve the overall safety of indoor UV tanning devices to protect adult consumers. As of July 31, 2016, legislation banning the use of indoor UV tanning devices by people younger than age 18 is already in place in numerous countries and several U.S. states:



- **Banned all indoor tanning—** Brazil and Australia.
- **Banned indoor tanning for all people younger than 18—** Austria, Belgium, Finland, France, Germany, Iceland, Italy, Norway, Portugal, Spain, and the United Kingdom, as well as California, Delaware, the District of Columbia, Hawaii, Illinois, Louisiana, Minnesota, Nevada, New Hampshire, North Carolina, Texas, and Vermont.
- **Banned indoor tanning for people younger than 18 unless they have a doctor's prescription—** Oregon and Washington.

A number of other U.S. states have legislation that imposes less stringent restrictions on the use of indoor UV tanning devices, but eight states have no legislation restricting the use of such devices: Alaska, Colorado, Iowa, Kansas, Montana, New Mexico, Oklahoma, and South Dakota.

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	unknown
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 Virus (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 forms of lymphoma	2.1
Human Immunodeficiency Virus (HIV)	Kaposi sarcoma and non-Hodgkin lymphoma	unknown
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)	Skin cancer	unknown

* where known

Data from Ref. (76)

Despite the knowledge that the three main types of skin cancer—basal cell carcinoma, squamous cell carcinoma, and melanoma—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 (67), and one in three adults in the United States reports experiencing at least one sunburn in the past 12 months (68). In addition, 6 percent of U.S. adults report using an indoor UV tanning device at least once in the past 12 months (69). The most recent data show that use of indoor UV tanning devices has declined among high school students, from 13 percent in 2013 to 7 percent in 2015, although more needs to be done to reduce this number even further (53, 70).

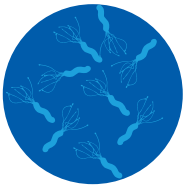
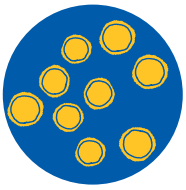
Continued exposures to UV radiation have fueled a rise in melanoma incidence rates over the past 3 decades (3), and researchers anticipate that the number of new U.S. melanoma cases diagnosed each year will rise dramatically in the coming decades if current trends continue, increasing from 65,647 in 2011 to 112,000 in 2030 (71). Thus, it is vital that individuals, families, communities, schools, workplaces, institutions, health care professionals, media, industry, government, and multinational bodies work together to develop and implement more effective policy changes and public education campaigns to reduce exposure to UV radiation. One policy change currently being considered by the FDA is a ban on the use of indoor UV tanning devices by individuals younger than age 18 (see sidebar on **Indoor Tanning Legislation**, p. 32). This measure could be particularly effective at reducing exposure to UV radiation given that recent research showed that placing age restrictions on the use of indoor UV tanning devices reduces the use of these devices by female high school students (72).

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**) (74-76). It is estimated to have been responsible for about 2 million of the 12.7 million new cases of cancer diagnosed

worldwide in 2008, with more than 90 percent of these cases attributable to just four pathogens: *Helicobacter pylori*, hepatitis B virus (HBV), hepatitis C virus (HCV), and human papillomavirus (HPV) (76). Therefore, individuals can significantly lower their risk 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**).

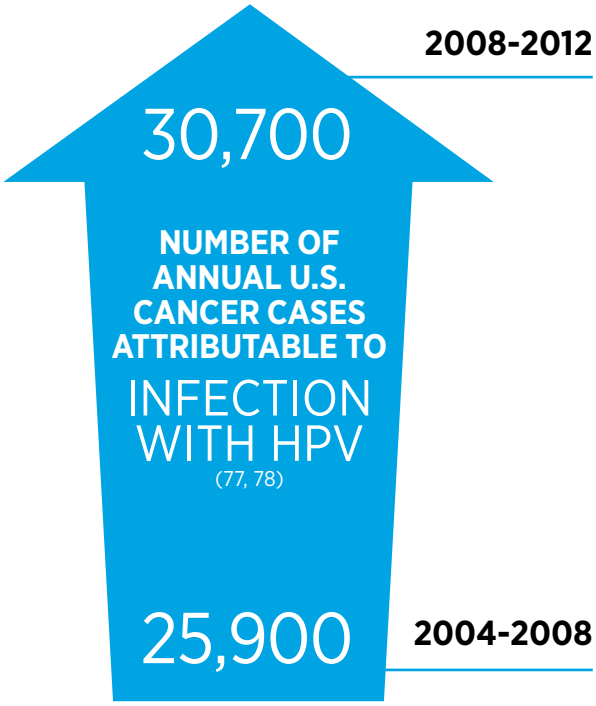
PREVENTING OR ELIMINATING INFECTION WITH THE FOUR MAIN CANCER-CAUSING PATHOGENS

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 three-dose course as a preteen.

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 (1).

Although there are strategies available to eliminate, treat, or prevent infection with *Helicobacter pylori*, HBV, HCV, and HPV, it is clear that these strategies are not being used optimally. For example, even though the CDC recommends screening all U.S. adults born from 1945 to 1965 for HCV infection and there are several therapeutics that can eliminate HCV infection, it is estimated that there are at least 3.5 million people in the United States currently infected with HCV (79). Given that infection with HCV is estimated to be responsible for 22 percent of cases of hepatocellular carcinoma (HCC)—the most common form of liver cancer—in U.S. adults age 68 or older (80), the burden of HCC could be significantly reduced through more effective implementation of HCV screening and treatment.

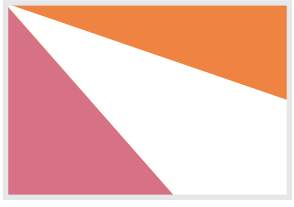
In addition, the development of strategies to increase uptake of the three FDA-approved HPV vaccines could have an immense impact on cancer prevention (see sidebar on **How Do the Three FDA-approved HPV Vaccines Differ?**). It is estimated that in the United States, more than 53,000 cases of cervical cancer and thousands of cases of other HPV-related cancers, including many anal, genital, and oral cancers, could be prevented if 80 percent of those



HOW DO THE THREE FDA-APPROVED HPV VACCINES DIFFER?

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

3 **FDA-approved vaccines can prevent infection** with some of these strains.



CERVARIX

- Protects against infection with HPV16 and HPV18.
- FDA approved in 2009.
- FDA approved for:
  - preventing cervical cancer and precancers.
  - vaccination of females ages 9 to 25.

GARDASIL

- Protects against infection with HPV16 and HPV18, as well as HPV6 and HPV11, which cause genital warts.
- FDA approved in 2006.
- FDA approved for:
  - preventing anal, cervical, vaginal, and vulvar cancers and precancers, as well as genital warts.
  - vaccination of males and females ages 9 to 26.

GARDASIL 9

- Protects against infection with HPV6, 11, 16, 18, 31, 33, 45, 52, and 58.
- FDA approved in 2014.
- FDA approved 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.

Information is current as of July 2016

Adapted from (24)

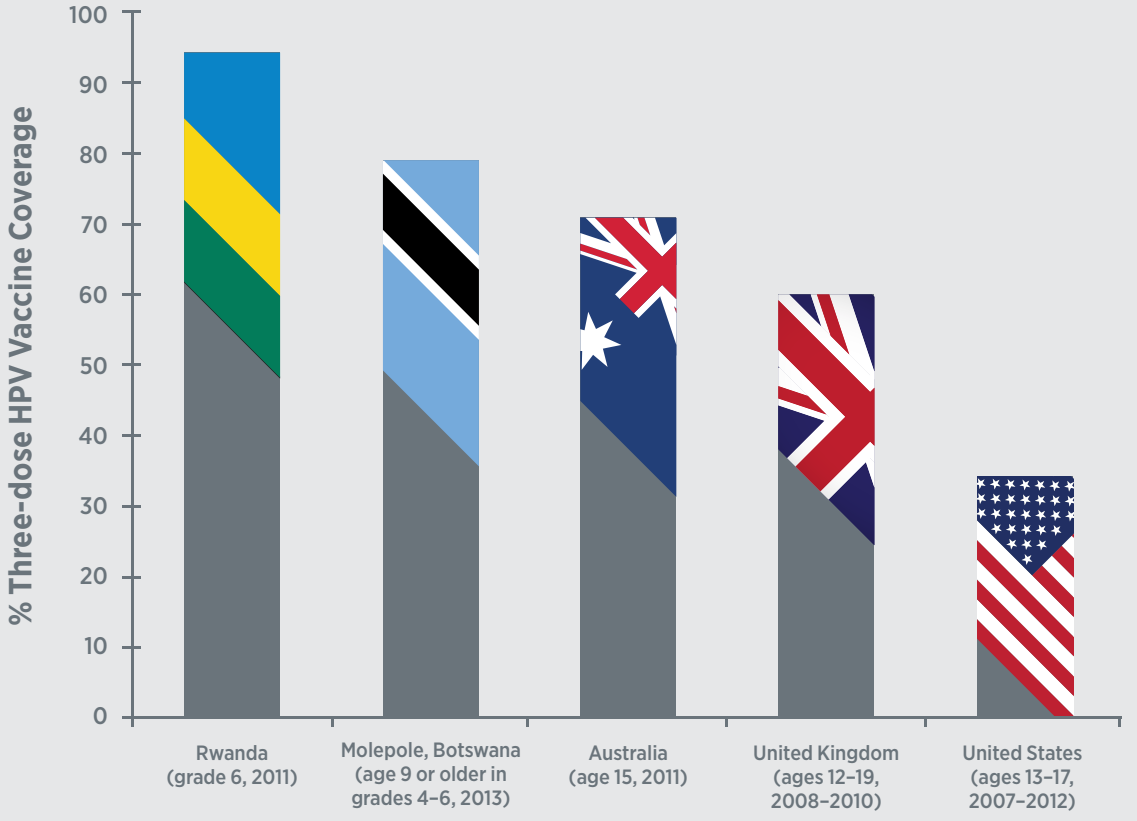
for whom HPV vaccination is recommended—girls and boys at age 11 or 12—were to be vaccinated (81). However, the most recent estimates from the CDC show that in 2014, only 40 percent of girls ages 13 to 17 and 24 percent of boys of the same age had received the full course of three or more doses of an HPV vaccine (82). This low coverage stands in stark contrast to three-dose HPV vaccine coverage in other countries (81, 83) (see **Figure 7**).

In 2011–2012,
847,000
noninstitutionalized U.S. adults were estimated to be chronically infected with HBV (79).

Several steps to address the low HPV vaccine coverage in the United States were recently recommended by the National Vaccine Advisory Committee (NVAC), a federal advisory committee that provides vaccine and immunization policy recommendations to the U.S. Department of Health and Human Services (85). Among the objectives outlined by the NVAC was the development of comprehensive communication strategies for physicians to encourage HPV vaccination at every opportunity. The need for these strategies is highlighted by recent data showing that many physicians recommend HPV vaccination inconsistently, behind schedule, or without urgency (86).

FIGURE 7

IN NEED OF A BOOST



The percentage of adolescent girls in the United States to have received the recommended three doses of the human papillomavirus (HPV) vaccine is very low compared with the percentages vaccinated in other high-income countries, such as Australia and the United Kingdom. Rwanda, a low-income country, has implemented a national, multisector, collaborative, school-based HPV vaccination program (81, 83). A trial of a school-based HPV vaccination program in Molepole, a traditional village in Botswana with a population of more than 60,000, was recently reported to have led to 79 percent of eligible girls receiving three doses of the HPV vaccine and to a nationwide rollout of the program in 2015 (84).

LIMIT EXPOSURES TO ENVIRONMENTAL RISK FACTORS

There are many other cancer risk factors in our environment, including environmental pollutants and occupational cancer-causing agents (87) (see **Figure 3**, p. 24). It can be difficult for people to avoid or reduce their exposure to many of these factors. Therefore, it is imperative that policies are put in place to ensure that everyone lives and works in a safe and healthy environment.

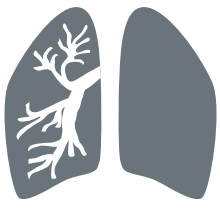
In the United States, some policies that help protect people from known cancer risk factors have been in place for several decades. For example, there are numerous policies to help prevent exposure to asbestos, which can cause mesothelioma, an aggressive type of cancer for which there remain few treatment options (88). There are also guidelines for reducing exposure to radon gas, which is released from rocks, soil, and building materials and is the second most common cause of lung cancer in the United States after cigarette smoking (89). That said, compliance with these guidelines is not mandatory. It is estimated that about one in every 15 U.S. homes has radon levels at or above 4 picocuries per liter of air, which is the level at which the U.S. Environmental Protection Agency (EPA) recommends taking action (89).

As we learn more about environmental and occupational cancer risk factors and identify segments of the U.S. population exposed to these, we need to develop and implement new and/or more effective policies. We also need to do more worldwide to limit exposure to well-established environmental and occupational cancer risk factors such as asbestos.

One environmental pollutant that was recently classified by the International Agency for Research on Cancer (IARC), an affiliate of the World Health Organization, as having the ability to cause cancer in humans, is outdoor air pollution (90). 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 of outdoor air pollution. We do know, however, the sources of much outdoor air pollution—emissions from motor vehicles, industrial processes, power generation, and the burning of solid fuels for domestic heating and cooking—and it is clear that new policy efforts to reduce the release of pollutants into the atmosphere are needed if we are to reduce the burden of cancer.

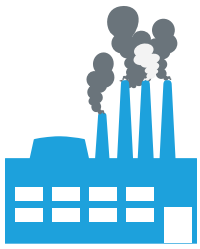
Growing knowledge of the environmental pollutants to which different segments of the U.S. population are exposed highlights new opportunities for education and policy initiatives to improve public health. For example, arsenic exposure is a well-established cause of bladder cancer. A recent study identified drinking water containing low-to-moderate levels of arsenic, obtained from shallow-dug private wells, as a potential contributor to the elevated incidence of bladder cancer that has been documented in New England for more than 5 decades (91).

In other cases, increasing knowledge of the presence of environmental pollutants in certain geographic regions emphasizes the need for more research to inform the future development and implementation of education and policy initiatives. For example, researchers recently found elevated levels of uranium and other heavy metals in abandoned mines in northeastern Arizona and are now investigating how this might affect nearby Native American communities (92).



5,000

U.S. lung cancer deaths could be prevented each year if radon levels in every home were reduced below the level at which the U.S. Environmental Protection Agency (EPA) recommends taking action (4 picocuries per liter of air) (89).



Five new research centers

to improve health in U.S. communities overburdened by pollution and other environmental factors that contribute to health disparities are being funded by a partnership between the National Institutes of Health (NIH) and the U.S. Environmental Protection Agency (EPA).

For more information go to: https://www.nih.gov/news-events/news-releases/new-nih-epa-research-centers-study-environmental-health-disparities

FINDING CANCER

In this section you will learn:

- Understanding of the biology 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 test; these recommendations are updated periodically to incorporate new evidence.
- Areas of disagreement among different recommendations highlight areas in which more research is needed.
- Some people are at increased risks for certain types of cancer and may need to take measures to reduce the risks.

The primary cause of cancer initiation and development is 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 genetic mutation acquisition (see **Figure 3**, p. 24), and 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 us with opportunities to develop screening strategies that allow us to detect, if present, precancerous lesions or cancer at an early stage of development (see **Figure 8**, p. 39). Precancerous lesions can be removed before they develop into 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 the patient treated successfully.

CANCER SCREENING

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 Screening Tests Exist**, p. 40). 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. Recommendations on how best to use these tests are discussed in the information to follow.

One area of intensive research investigation aims to gain a deeper understanding of the biology of precancerous lesions (93, 94). The goal is that as we learn more about the genetic, molecular, and cellular characteristics of precancerous lesions, we can develop new screening tests and cancer prevention therapeutics, as well as more precisely identify those for whom cancer screening and cancer prevention therapeutics would be beneficial.

WHO SHOULD BE SCREENED?

Screening to detect cancer before an individual shows signs or symptoms of the disease for which he or she is being screened has many benefits, but it can also result in unintended adverse consequences (see sidebar on **Cancer Screening**, p. 41). Thus, population-level use of a cancer screening test must not only decrease deaths from the screened cancer, but it must also 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.

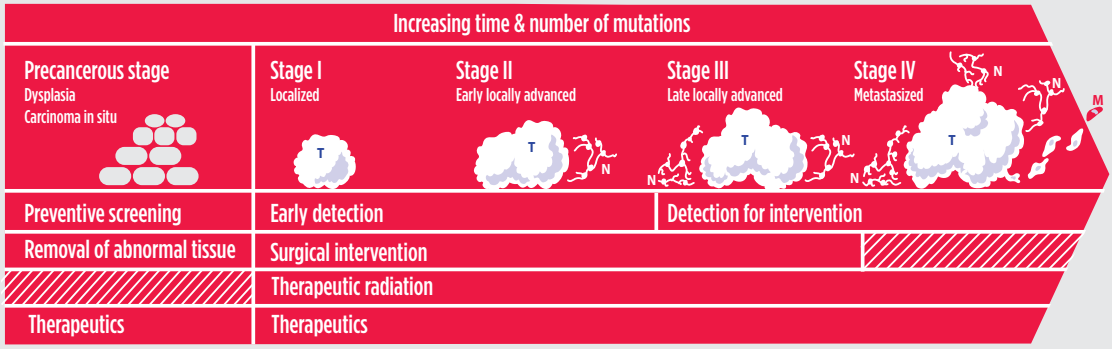
In the United States, an independent group of experts convened by the Agency Healthcare Research and Quality of the US Department of Health and Human Services rigorously evaluates data regarding the benefits and potential risks of cancer screening tests to make evidence-based recommendations about the routine use of these tests. These volunteer experts form the U.S. Preventive Services Task Force (USPSTF). In addition to considering evidence regarding potential new screening programs, the USPSTF re-evaluates 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 makes 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 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 when and for which cancers they should be screened. Nevertheless, there is more consensus among recommendations than disagreement (see sidebar on **Consensus Among Cancer Screening Recommendations**, p. 42). 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 are only one consideration when a person makes decisions about which cancers he or she should be screened for and when. A consideration for some people is whether a screening test is covered by his or her health insurance. The enactment of the Patient Protection and Affordable Care Act of 2010, also known as "Obamacare," increased the number of people covered by health insurance. It also includes a provision that requires qualified health insurance plans offered through health insurance exchanges, health insurance plans not designated as grandfathered, and Medicare to cover the costs of cancer screening tests recommended as grade A or B by the USPSTF. Individuals should check their own plans to see if they are covered. A consequence of this legislation is broader access to recommended screening tests for more people. For example, one recent study estimates that the enactment of this legislation enabled 6.8 million low-income women to gain access to health insurance, which should lead to increases in levels of cancer screening among this population (95). Further research is needed to confirm this result.

FIGURE 8 POINTS OF INTERVENTION

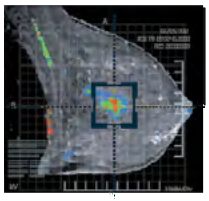


Many cancers are progressive in nature. In the example depicted here, an initial genetic mutation can lead to normal cells taking on precancerous characteristics. As these cells multiply and acquire more genetic mutations, the precancerous lesion becomes increasingly dysplastic, or abnormal. Over time, as additional genetic mutations accumulate, the dysplastic precancerous lesion may evolve into a cancerous lesion, then spread to nearby lymph nodes and, as it becomes more advanced, ultimately metastasize. Screening tests—such as the Pap test and colonoscopy—can be used to prevent cancer because they can find precancerous lesions, which can then be removed before they develop into cancerous lesions either through surgery or with the use of certain therapeutics (see **Supplemental Table 1**, p. 130). Use of other screening tests, such as mammography, aims to find cancer at an early stage, when it is more likely that the patient can be treated successfully. The treatment a patient receives depends on numerous factors, including the type of cancer and the stage of disease at which diagnosis occurred, but it can include surgery, radiotherapy, chemotherapy (both cytotoxic and molecularly targeted), and/or immunotherapy. Treating a precancerous lesion or early stage cancer detected by screening is sometimes called cancer interception.

CANCERS FOR WHICH SCREENING TESTS EXIST

Highlighted here are cancer screening tests that have been used in the clinic to screen generally healthy individuals. When to use these tests and in whom is discussed elsewhere (see **Who Should Be Screened?, p. 38).**

BREAST CANCER



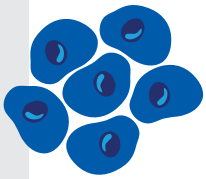
Screening mammogram: Uses X-rays to image the breast.

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 two-dimensional, but some machines generate three-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



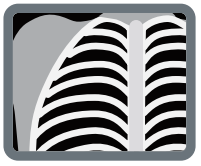
Pap test: Samples cervical cells, which are analyzed under a microscope to look for abnormalities.

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.

LUNG CANCER



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

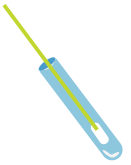
Can detect lung cancers that are not causing symptoms. These cancers can be at any stage of development, but the aim of screening is to find them at the earliest possible stage.

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.

COLORECTAL CANCER

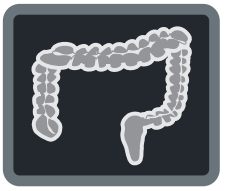


Stool tests: Some test for the presence of red blood cells in stool samples. Others test for both red blood cells and certain genetic mutations linked to colorectal cancer.

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

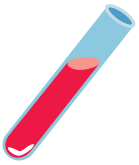
Flexible sigmoidoscopy and colonoscopy: Both use a thin, flexible, lighted tube with a small video camera on the end to allow physicians to look at the lining of certain parts of the colon and rectum.

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 (see **Increasing Options for Colorectal Cancer Screening**, p. 57).

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

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 spot (see **Figure 8**, p. 39).

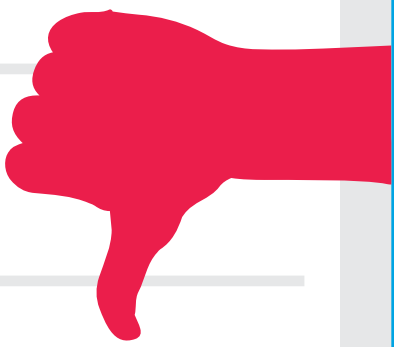
Reduced incidence of advanced disease. Screening tests that detect developing cancers can reduce the individual's risk of being diagnosed with the screened cancer at a stage when it has spread to other parts of the body (see **Figure 8**, p. 39).

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 (USPSTF) 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 screen 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 screen 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 are difficult to quantify.

Adapted from (1)

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, 2016, 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 Urological Association (AUA). Not all of the professional societies have recommendations for every cancer screening test.

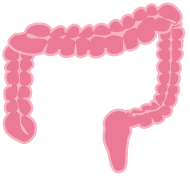
BREAST CANCER

There is consensus among the 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.

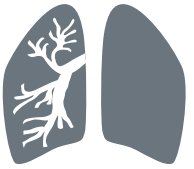


COLORECTAL CANCER

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, however, recommend certain approaches over others. The overall message 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 little consensus among the ACS, ACP, AUA, NCCN, and USPSTF, with recommendations ranging from do not screen at all to screen regularly. That said, the ACS, ACP, and AUA all recommend 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.

To find out more about cancer screening recommendations for people who fall outside the age groups highlighted here or for people who are at increased risks for certain cancers see: http://www.uspreventiveservicestaskforce.org/, http://www.cancer.org/, http://m.acog.org/, https://www.auanet.org/, https://www.acponline.org/, and https://www.nccn.org/.

TABLE 5 INHERITED CANCER RISK

Cancers	Syndrome	Associated Gene(s)
Leukemias and lymphomas	Ataxia telangiectasia	ATM
Basal cell carcinoma	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	Familial adenomatous polyposis (FAP)	APC
Melanoma and pancreatic cancer	Familial atypical multiple mole–melanoma syndrome (FAMM)	CDKN2A
Retinal cancer	Familial retinoblastoma	RB1
Leukemia	Fanconi's anemia	FACC, FACA
Kidney cancer and uterine fibroids	Hereditary leiomyomatosis and renal cell cancer	FH
Pancreatic cancer	Hereditary pancreatitis/familial pancreatitis	PRSS1, SPINK1
Leukemias, breast, brain, and soft tissue cancers	Li-Fraumeni syndrome	TP53
Colorectal and endometrial cancers	Lynch syndrome	EPCAM, MLH1, MSH2, MSH6, PMS2
Pancreatic cancers, pituitary adenomas, benign skin, and fat tumors	Multiple endocrine neoplasia 1	MEN1
Thyroid cancer and pheochromacytoma	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

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 when deciding when and for which cancers to be screened (see sidebar on **Cancer Screening**, p. 41). A 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 **Congressman Donald Payne** did (see p. 44). Given that these factors can vary over a person's lifetime, it is important that individuals continually evaluate their cancer screening plans and update them if necessary.

Some individuals are at increased risk of certain cancers because they inherited a cancer-predisposing genetic mutation (see **Table 5**) (96). If an individual has a family

About 5%–10%

of new U.S. cancer cases are linked to inherited cancer-predisposing genetic mutations (22).

RAISING AWARENESS ABOUT COLORECTAL CANCER SCREENING AND CANCER HEALTH DISPARITIES

THE HONORABLE DONALD M. PAYNE, JR. // U.S. REPRESENTATIVE FOR NEW JERSEY'S 10TH CONGRESSIONAL DISTRICT // CO-CHAIR OF THE CONGRESSIONAL MEN'S HEALTH CAUCUS // AGE 57

Witnessing my father's heartbreaking battle with colorectal cancer was one of the most difficult times in my life. On the other hand, it made me passionate about increasing awareness of the benefits of colorectal cancer screening, particularly in communities disproportionately affected by the disease. It also drove me to work toward the elimination of cancer health disparities and led me to be vigilant about my own cancer screening.

My father, the late Congressman Donald M. Payne, was a member of Congress for 23 years. He was very well educated, but neither he nor I realized the importance of colorectal cancer screening. As a result, he was not tested in time to prevent his cancer or even to detect it at an early stage, when it could have been more easily treated. He ultimately lost his battle with colorectal cancer in March 2012. I have often said that had he been screened earlier, he would still be with us today.

After my father's diagnosis with colorectal cancer, I set out to educate myself about the disease. I learned that experts recommend that men and women at average risk for colorectal cancer begin screening for the disease at age 50. I also learned that colorectal cancer affects the African-American community more deeply than it does other communities and that some experts recommend African Americans start screening at age 45.

Given my father's experience and what I had learned in my own research about colorectal cancer, I decided to have my first colonoscopy in December 2012, the day I turned 54. It was a good decision because the doctor found and removed 13 polyps, or precancerous growths, during the procedure. I was shocked to learn this, but I was glad to have caught the polyps before they became cancerous.

When I went back the following year for a second colonoscopy, the doctor found and removed another three polyps. Since then, I have had a colonoscopy every year on my birthday. I tell people it is my birthday present to myself because I know routine screenings are essential for maintaining my health.

As a result of my experiences, I am dedicated to spreading the word about how colorectal cancer screening saves lives. I speak to a lot of communities—at community health centers, on neighborhood corners, and at places of worship—about the fact that colorectal cancer is highly preventable, but you have to catch it early. I tell people about the need for testing, and I try to dispel the notion that the screening process is painful and extremely unpleasant. It's a moment of discomfort, but it can save your life. By talking about colorectal cancer, I hope to remove the stigma that is attached to the disease and the screening tests.

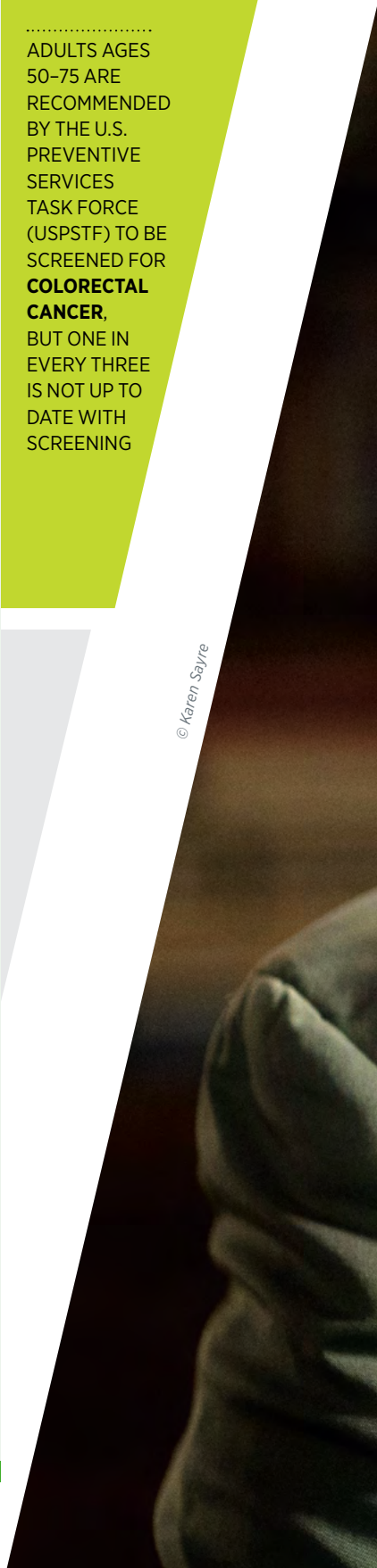
During my work to raise awareness about colorectal cancer screening, I have come to realize that men oftentimes think they are invincible. However, we need to be more proactive about our health so that we can enjoy our later years and so that we can give ourselves and our families the security we deserve.

As co-chair of the Congressional Men's Health Caucus, I have a great opportunity to raise awareness of the importance of preventive care among men and to help reduce health disparities across diseases, particularly those that touch so many lives, like cancer. Improving outcomes for communities disproportionately affected by cancer not only means spreading awareness about preventive care, but it also means educating people in these communities about the importance of participating in clinical trials.

Although clinical trials are at the heart of the process for bringing new medicines to patients, African Americans and other minorities remain significantly underrepresented in these trials. Encouraging minority participation in clinical research is important so that all communities, regardless of race, ethnicity, or socioeconomic status benefit from promising new treatments.

My role as co-chair of the Congressional Men's Health Caucus has also afforded me the chance to more effectively advocate for getting the National Institutes of Health and the Centers for Disease Control and Prevention the funding they need to push forward research and screenings to save and improve more lives. As a lawmaker, I have the responsibility to make sure that people do not experience what my family went through. We must continue to educate people about the importance of funding for research and prevention in our fight against cancer.

ADULTS AGES 50–75 ARE RECOMMENDED BY THE U.S. PREVENTIVE SERVICES TASK FORCE (USPSTF) TO BE SCREENED FOR **COLORECTAL CANCER**, BUT ONE IN EVERY THREE IS NOT UP TO DATE WITH SCREENING



© Karen Sayre

> As co-chair of the Congressional Men's Health Caucus, I have a great opportunity to raise awareness of the importance of preventive care among men and to help reduce health disparities across diseases ...

TABLE 6

SURGERIES FOR THE PREVENTION OF CANCER

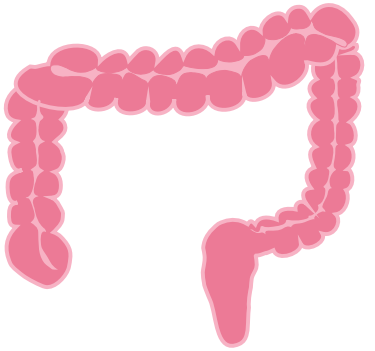
Genetic Mutation(s)	Cancer	Technique	Removes
APC	Colon Cancer	Colectomy	Colon/large intestine
BRCA1 or BRCA2	Breast Cancer	Mastectomy	Breasts
BRCA1 or BRCA2	Ovarian Cancer	Salpingo-oophorectomy	Ovaries and fallopian tubes
CDH1	Stomach Cancer	Gastrectomy	Stomach
RET	Medullary thyroid cancer	Thyroidectomy	Thyroid

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. 47). 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 (see sidebar on **Direct-to-Consumer Genetic Testing**, p. 47).

In addition to cancer-predisposing genetic mutations, a number of medical conditions increase a person's risk for certain types of cancer. For example, ulcerative colitis and Crohn disease increase an individual's risk for colorectal cancer, and a complication of gastroesophageal reflux disease (Barrett esophagus) increases risk for esophageal adenocarcinoma (97, 98). These are all relatively rare conditions, but much more prevalent medical conditions also increase risks for certain cancers. For example, type 2 diabetes, which affects 9.5 percent of U.S. adults age 18 or over (20), increases an individual's risk of developing liver, pancreatic, and endometrial cancers (99, 100).

If a person is at increased risk for developing a certain type or types of cancer, he or she can 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 smoking cessation. 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; for example, the American College of Gastroenterology (although not the USPSTF) recently put forth recommendations about using endoscopy to screen people diagnosed with Barrett esophagus for precancerous lesions, esophageal lesions, and/or esophageal cancer (101). Yet others may consider taking a preventive medicine or having risk-reducing surgery (see **Table 6** and **Supplemental Table 1**, p. 130).

As we learn more about the genetic, molecular, and cellular characteristics of precancerous lesions, 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 (26).



The USPSTF recently recommended that

adults ages 50–59

who have a 10% or greater 10-year risk for developing cardiovascular disease, are not at increased risk for bleeding, have a life expectancy of at least 10 years, and are willing to take low-dose aspirin daily for at least 10 years, start taking low-dose aspirin to prevent cardiovascular disease as well as colorectal cancer (102).

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

Among the factors to consider are whether, in your family, there is one or more of the following:

- many cases of an uncommon or rare type of cancer (such as kidney 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); and
- one or more members with cancers in both of a pair of organs (such as both eyes, both kidneys, or both breasts);
- more than one childhood cancer in a set of siblings (such as sarcoma in both a brother and a sister);
- members with a type of cancer usually occurring in the opposite sex (such as breast cancer in a man).

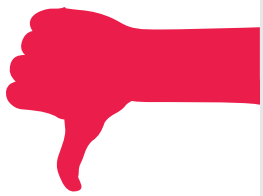
Adapted from: http://www.cancer.org/cancer/cancercauses/geneticsandcancer/heredity-and-cancer.

DIRECT-TO-CONSUMER GENETIC TESTING

Direct-to-consumer (DTC) genetic tests are marketed directly to consumers, in contrast to tests that are ordered by a physician for a patient. This growing form of testing, also known as at-home testing, allows a consumer or patient to obtain access to his or her genetic information without necessarily involving a doctor or insurance company in the process. Below are a number of important facts about DTC genetic tests.

Potential Benefits of Using DTC Genetic Tests
These tests may encourage and empower consumers to take a proactive role in their health care.

Potential Risks of Using DTC Genetic Tests
These tests may mislead or misinform people about their health status.



DTC Genetic Tests and the FDA
DTC tests that claim to provide only information such as a person's ancestry or genealogy are not regulated by the U.S. Food and Drug Administration (FDA). In February 2015, however, the FDA authorized marketing of the first DTC genetic test: 23andMe's Bloom Syndrome carrier test. This test can help determine whether a healthy person has a variant in a gene that could lead to his or her children inheriting this serious disorder.

FDA APPROVED

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

Adapted from (24)

SAVING LIVES THROUGH RESEARCH

In this section you will learn:

- From Aug. 1, 2015, to July 31, 2016, the FDA approved 13 new therapeutic agents for treating certain types of cancer, one new cancer screening test, one new diagnostic test, two new diagnostic imaging agents, and a new medical device.
- During the same period, the FDA authorized new uses for 11 previously approved anticancer therapeutics.
- Different immunotherapeutics work in different ways to unleash the power of a patient's immune system to fight cancer.
- Palliative care, given alongside cancer treatment and through the balance of life, can improve quality of life for patients and survivors.

The dedicated efforts of individuals working throughout the cycle of biomedical research (see **Figure 9**, p. 49) have led to extraordinary advances across the continuum of clinical care that are improving and saving lives in the United States and worldwide.

BIOMEDICAL RESEARCH

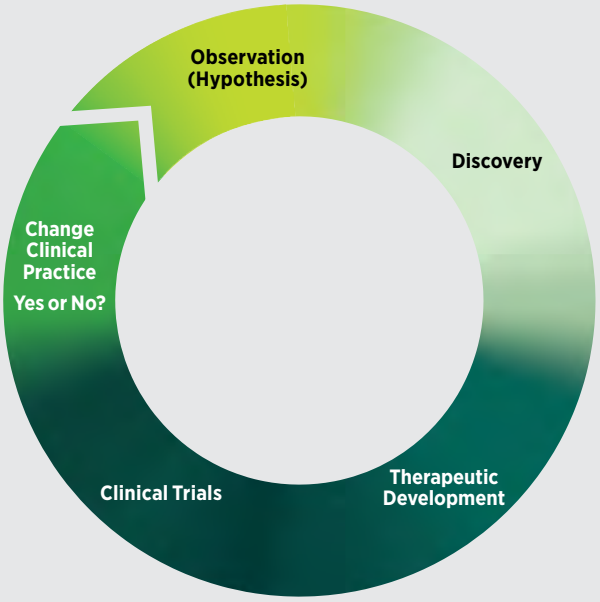
Biomedical research is an iterative cycle, with each discovery building on knowledge gained from prior discoveries (see **Figure 9**, p. 49). In recent years, the cycle has become more efficient as the pace of discoveries has increased, and new disciplines have been integrated into the biomedical research enterprise (see sidebar on **Biomedical Research: What It Is and Who Conducts It**, p. 50). As a result of these changes, the pace at which research improves lives, like the lives of **Harrison McKinion** and his family (see p. 52), has accelerated. It is anticipated that this rapid pace of progress will continue or speed up even more in the foreseeable future (see **Anticipating Future Progress**, p. 100).

The biomedical research cycle is set in motion when discoveries with the potential to affect the practice of medicine and public health are made by researchers in any area of biomedical research, including laboratory research, population research, clinical research, and clinical practice. The discoveries lead to questions, or hypotheses, which are tested by researchers conducting studies in a wide array of models, ranging 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 or preventive intervention, they can feed back into the cycle by providing new discoveries that lead to more hypotheses, or they can affect the practice of medicine in other ways, for example, by allowing for more precise classification of a patient's disease, which has the potential to influence treatment decisions (see sidebar on **Reclassification of Brain Tumors**, p. 51).

Nothing Happens Without You.

When cancer patients and their families consent to share their tissues and information, the pace at which new advances are made is accelerated.

FIGURE 9 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 (see sidebar on **Biomedical Research: What It Is and Who Conducts It**, p. 50). 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. 54). 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 sidebar on **Phases of Clinical Trials**, p. 55). 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 improve 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 Ref. (24)

After a potential therapeutic target is identified, it takes several years of hard work before a candidate therapeutic is developed and ready for testing in clinical trials (see sidebar on **Therapeutic Development**, p. 54). 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 novel 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.

In oncology, treatment clinical trials often add the investigational anticancer therapeutic to the current standard of care. These types of clinical trials have traditionally been done in three successive phases, each with an increasing number of patients (see sidebar on **Phases of Clinical Trials**, p. 55).

As a result of recent, research-powered 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), researchers, regulators, and the pharmaceutical industry have been able to develop new ways of conducting clinical trials. The new approaches aim to streamline the development of new anticancer therapeutics by matching the right therapeutics with the right patients earlier, reducing the number of patients that 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.

At the regulatory level, the FDA has implemented several changes that have altered how clinical trials can be conducted and reviewed in an effort to reduce the length

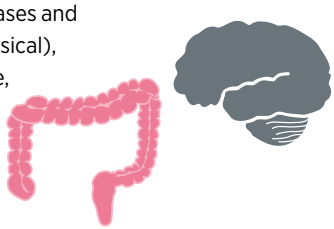
of time it takes to obtain a clear result from a clinical trial (see sidebar on **FDA's Expedited Review Strategies**, p. 56). An increasing number of anticancer therapeutics are being approved by the FDA using the most recently introduced of these review strategies—breakthrough therapy designation. A key part of this review strategy is that the FDA engages with those developing the investigational therapeutic early in the clinical trials process and provides continued guidance throughout the review period. It is sometimes used alongside other expedited review strategies, such as accelerated approval.

One of the main changes to the way in which clinical trials are conducted is the increasing use of genomics and adaptive trial designs to identify the patients most likely to benefit from an investigational anticancer therapeutic. These approaches aim to reduce the number of patients that need to be enrolled in a clinical trial to determine whether the therapeutic being evaluated is effective. They largely fall into one of two clinical trial designs: "basket" studies and "umbrella" studies (see **Figure 10**, p. 57). Basket trials test one given therapeutic on a group of patients who all have the same type of genetic mutation, regardless of the anatomic site of the original

BIOMEDICAL RESEARCH: WHAT IT IS AND WHO CONDUCTS IT

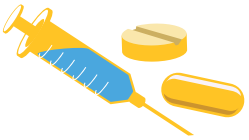
Biomedical research, as defined by the Organization for Economic Cooperation and Development (OECD), comprises:

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



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

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



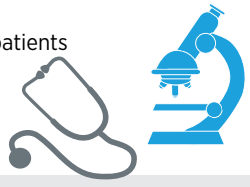
Biomedical researchers are often categorized by the type of work they do, although some individuals perform several types of work and can be included in a number of categories. The types of biomedical researchers include, but are not limited to, the following:

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

Clinical researchers conduct clinical trials; study a particular patient or group of patients, including their behaviors; or use materials from humans, such as blood or tissue samples, to learn about the way the healthy body works, disease, or response to treatment(s).

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

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



Adapted from (1)

cancer. Umbrella trials test multiple therapeutics across multiple genetic mutations on a group of patients, all of whom have cancer arising in the same anatomic site.

As our knowledge of cancer biology grows at an ever-quickening pace, continued and increased dialogue among researchers, regulators, and the pharmaceutical industry is essential to provide the right patients access to the best anticancer therapeutics that have been proven to be safe and highly effective in well-designed, well-conducted clinical trials at the earliest possible time (105).

Dialogue among researchers, regulators, and the pharmaceutical industry is also important as physician-scientists look to use genomics to identify patients who might benefit from therapeutics not previously FDA approved for their type of cancer, an approach known as drug repositioning or drug repurposing.

One patient who is benefiting from drug repositioning is **Luke Theodosiades**, who was just 11 years old when he was diagnosed with acute lymphoblastic leukemia (ALL) (see p. 58). After his leukemia did not respond well at all to intensive standard-of-care chemotherapy, Luke's team of physicians at Children's Hospital of Philadelphia were very concerned and pursued a specialized genomic analysis of his leukemia cells performed by researchers at the University of New Mexico. This analysis found that his leukemia cells had undergone genetic recombination (see sidebar on **Genetic Mutations**, p. 20), resulting in the fusion of two genes (GOLGA5 and JAK2). The GOLGA5-JAK2 fusion gene generated a new protein that was driving the multiplication of Luke's leukemia cells and likely conferred resistance to his initial chemotherapy. Because JAK2 is a protein targeted by ruxolitinib (Jakafi), which was first approved by the FDA in 2011 for treating adults with myelofibrosis, Luke's physicians added ruxolitinib to his treatment regimen. After several months of combination therapy, no leukemia cells with the GOLGA5-JAK2 fusion protein were detectable in Luke's bone marrow, making him eligible to receive other treatments to maintain long-term remission.

As of July 31, 2016, breakthrough therapy designation has been awarded to

45

anticancer therapeutics since its introduction in 2012; 18 of these have received FDA approvals after being designated breakthrough therapies.

RECLASSIFICATION OF BRAIN TUMORS

23,770 NEW CASES

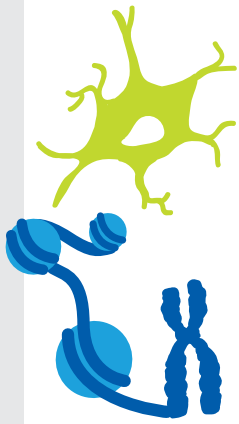
16,050 DEATHS

Researchers estimate that 23,770 new cases of brain and other nervous system cancers will be diagnosed in the United States in 2016, and that there will be 16,050 deaths from these types of cancers (3).

There are many types of brain and central nervous system tumors. Most oncologists use the World Health Organization (WHO) classification system to identify which of the many types of brain tumors a patient has. This information is vital to physicians and their patients as they understand the patient's outlook and decide which treatments are the best options.

In May 2016, the WHO updated the brain and central nervous system tumor classification system (103).

The previous classification system was based on identifying the cell type in which the tumor arose and how closely the cancer cells resemble the cell of origin (104).



The new classification system integrates molecular information about a patient's tumor with information on the cell of origin and how the cells look compared with the cell of origin (103). This reclassification was made possible by research that revealed the genetic and epigenetic variability among tumors previously thought to be of the same type.

The new classification system will allow physicians to more precisely diagnose and treat patients.

"...we are truly grateful for the research that led to imatinib and other drugs like it that have kept our son alive..."

CONTINUING TO BATTLE LEUKEMIA BECAUSE OF RESEARCH

A MESSAGE FROM GINGER AND STEVE MCKINION, HARRISON'S PARENTS

HARRISON MCKINION \\ AGE 14 \\ WAKE FOREST, NORTH CAROLINA

BCR-ABL1–POSITIVE ALL COMPRISES 2% TO 5% OF **CHILDHOOD ALL**

© Art Howard

Our son Harrison was diagnosed with acute lymphoblastic leukemia (ALL) in December 2011. When 4 weeks of chemotherapy did not eliminate the leukemia from Harrison's bone marrow, his doctors looked at the genome of the leukemia cells. They found an alteration recently detected in leukemia cells from other children whose ALL did not respond to chemotherapy. Harrison was the first child with ALL to have a drug targeted to the effects of the genomic alteration, the tyrosine-kinase inhibitor imatinib (Gleevec), added to his chemotherapy. It put him into complete remission. Although he has recently had a relapse of the leukemia in his central nervous system, Harrison's doctors have turned to second-generation tyrosine-kinase inhibitors, and we are hoping they will help the way imatinib did.

Harrison's diagnosis with ALL came just a few days after his 10th birthday. He had always been a very energetic child, constantly outside playing sports. But for about 2 months before the diagnosis, he hadn't been feeling his usual self. Over that time, he gradually felt worse. Harrison became more and more lethargic, started having night sweats, and became very pale.

Thinking he had a virus, we took him to the pediatrician. The pediatrician sent us straight to the emergency room (ER) at Wake Med, telling us Harrison either had a virus or leukemia, and further tests were needed immediately to distinguish between the two.

A blood test in the ER confirmed that Harrison had leukemia, and he was transferred right away to North Carolina Children's Hospital. Just 2 days later, he started the intensive induction chemotherapy that is standard treatment for pediatric ALL.

The goal of induction chemotherapy is to achieve complete remission, and so the drugs that they use are very strong. It was a really difficult time for the whole family, and the chemotherapy took its toll on Harrison's body. About 2 weeks into the treatment, he had a stroke and multiple seizures. He was in the pediatric intensive care unit for 10 days, and we didn't know if he would live.

After 4 weeks of chemotherapy, we found out there were almost as many leukemia cells in Harrison's bone marrow as there had been when he was diagnosed. He was in the small percentage of patients who do not go into remission after induction chemotherapy. We were devastated.

Harrison's doctors began looking for answers as to why he was not in remission. One thing they did was look at the genome of the leukemia cells. They found the cells contained a recently reported chromosomal translocation found in cases of pediatric ALL that did not respond to induction chemotherapy.

Harrison's doctors contacted the researchers who had first reported the chromosomal translocation, and together they decided to add imatinib to the chemotherapy regimen because imatinib targets the effects of the chromosomal translocation.

About a week after starting imatinib, Harrison was in remission. The day we found out—January 24, 2012—was amazing. We were very tense waiting for the test results, but the doctor came in and said, "We have a touchdown." All the nurses, oncologists, and patients in the clinic erupted in cheers and clapping.

Harrison continued through the standard chemotherapy protocol for pediatric ALL, which ended in April 2015. Throughout that time and until the relapse in his central nervous system was discovered at the end of June [2016] he took imatinib once a day.

The doctors think the relapse occurred because imatinib does not penetrate into the central nervous system very well. So they switched him to dasatinib (Sprycel), a second-generation tyrosine-kinase inhibitor that penetrates the central nervous system better than imatinib. This drug knocked down the number of leukemia cells but did not eliminate all of them. As a result, Harrison has just finished a course of high-dose chemotherapy and another drug that targets the effects of the chromosomal translocation, nilotinib (Tasigna).

We are hoping that this plan will put Harrison into complete remission again and allow him to move on to the consolidation phase of treatment for his type of leukemia.

We are telling Harrison's story because we are truly grateful for the research that led to imatinib and other drugs like it that have kept our son alive and have the potential to put him back into complete remission. His doctors told us if he had been diagnosed just 6 months earlier, he would not have survived because the research knowledge that led them to their treatment decisions would not have been there. With greater public and private support for research, we believe that more children will survive their cancers.

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.

IND

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)

Additional genomics research has identified JAK2 gene rearrangements in leukemia cells from other children with ALL (106). However, before ruxolitinib can become part of the standard treatment for children with this genomically defined form of ALL, it must be proven to be effective in well-designed, well-conducted clinical trials.

The advent of technologies that allow researchers to interrogate all of the changes in a patient's cancer at one time and to look at all of the proteins in a diseased or healthy tissue simultaneously has revolutionized cancer research and is poised to do so for other diseases as well. Physicians and researchers are beginning to apply the knowledge gained from this research and use it to benefit patients like Luke Theodosiades, as well as Zach Witt, Warren Ringrose, Rita Porterfield, and Maryann Anselmo [all of whom were featured in the *AACR Cancer Progress Report 2015* (24)].

However, as we generate more data about all aspects of a patient's cancer and look to integrate this with the patient's baseline and long-term medical information, it becomes difficult to convert all of these various data into effective treatment decisions, because physicians are literally swimming in a sea of data. The enormous amount of data is both the problem and a potential solution (see **Figure 11**, p. 60).

Recognizing this paradox, several groups have independently started different efforts to address this challenge posed by the explosion of genomic information and the ability to link it to the clinical outcomes of the patients whose tumors have been genetically sequenced. Many of these groups are in the early stages of developing these efforts.

The analysis of the treasure trove of sequencing data has also revealed that the majority of tumors carry mutations that occur very infrequently. If we are to discover which of these mutations actually fuel tumor growth and to develop precision therapeutics that target the consequences of these mutations, many more patient samples will need to be sequenced.

In fact, a comprehensive analysis estimated that to discover all mutations that generate potential therapeutic targets in a patient population would require several thousand patients each with the same host of mutations (111). This analysis underscores the need for even more and bigger data than we currently have, as well as the tools necessary to convert the data into real knowledge that could inform patient treatment.

PHASES OF CLINICAL TRIALS

Clinical trials evaluating potential new anticancer therapeutics have traditionally been done in successive phases, each with an increasing number of patients.

PHASE I	Phase I studies are designed to determine the optimal dose of an investigational therapy and how humans process it, as well as to identify any potential toxicities. These first-in-human studies can also demonstrate early efficacy, or clinical results.
PHASE II	Phase II studies are designed to determine initial efficacy of an investigational therapy in a particular disease or selected group of patients, in addition to continually monitoring for adverse events or potential toxicities.
PHASE III	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	Phase IV studies are also known as post-marketing studies. They are conducted after a therapy is provisionally approved by the FDA and provide additional effectiveness or "real-world" data on the therapy.

Adapted from (1)

PROGRESS ACROSS THE CLINICAL CANCER CARE CONTINUUM

The hard work of individuals throughout the biomedical research cycle constantly powers the translation of discoveries to new medical products for cancer prevention, detection, diagnosis, treatment, and care (see **Figure 9**, p. 49).

In the 12 months spanning Aug. 1, 2015 to July 31, 2016, the FDA approved 18 new medical products—13 new anticancer therapeutics, one new blood-based companion diagnostic test, one new cancer screening test, two new diagnostic imaging agents, and a new medical device (see **Table 1**, p. 10). During this period, the FDA also approved new uses for 11 previously approved anticancer therapeutics, including obinutuzumab (Gazyva).

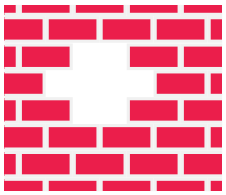
In February 2016, the FDA approved obinutuzumab for use in combination with the cytotoxic chemotherapeutic bendamustine to treat certain patients with follicular lymphoma, which is the second-most common form of non-Hodgkin lymphoma diagnosed in the United States. This approval followed its November 2013 approval for treating chronic lymphocytic leukemia (CLL), which was highlighted in the *AACR Cancer Progress Report 2014* (1). The approval

FDA'S EXPEDITED REVIEW STRATEGIES

The U.S. Food and Drug Administration (FDA) has developed four evidence-based strategies to expedite assessment of therapeutics for life-threatening diseases like cancer.

Accelerated approval. Accelerated approval is based on assessing the effect of a therapeutic at an earlier stage by using a surrogate endpoint. Any therapeutic approved in this way must undergo additional testing following approval to verify that it provides clinical benefit. Atezolizumab (Tecentriq) for the treatment of advanced urothelial carcinoma (the most common form of bladder cancer) was approved under this pathway in May 2016 (see p. 87).

Fast track. This designation is given to therapeutics that fill an unmet medical need and can be granted solely on the basis of preclinical data or data from nonhuman studies. Fast track applications may be evaluated through a "rolling" or continual review procedure, rather than waiting until study completion. Nivolumab (Opdivo) for the treatment of advanced renal cell carcinoma (the most common form of kidney cancer) was approved through fast track in November 2015 (see p. 83).



Breakthrough therapy. A therapeutic that shows substantial improvement over available treatment in early clinical studies can receive breakthrough therapy designation, making it eligible for all features of fast track designation (see above) and additional guidance from the FDA throughout the drug development process. One example of a therapeutic that was FDA approved, in April 2016, after receiving a breakthrough therapy designation is venetoclax (Venclexta) for the treatment of chronic lymphocytic leukemia (see p. 75).

Priority review. Therapeutics that have the potential to significantly improve safety or effectiveness may be granted priority review after all clinical trials are completed. This allows the therapeutic to be assessed within 6 months as opposed to the standard 10 months. Alectinib (Alecensa) was granted priority review and approved in December 2015 for the treatment of certain patients with lung cancer (see p. 70).

Adapted from (1)

of obinutuzumab for treating follicular lymphoma was based on the results of a phase III clinical trial, which showed that adding obinutuzumab to bendamustine more than doubled the median time to disease progression for patients whose disease had progressed despite treatment that included rituximab (Rituxan) (112).

New FDA-approved medical products are used alongside those already in the physician's armamentarium. Thus, most patients with cancer are treated with a combination of surgery, radiotherapy, chemotherapy (including both cytotoxic chemotherapeutics and molecularly targeted therapeutics), and/or immunotherapy (see **Supplemental Table 2**, p. 131, and **Supplemental Table 3**, p. 134).

The following discussion primarily highlights recent FDA approvals that are improving lives by having an effect across the continuum of clinical cancer care.

Cancer Prevention and Detection

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 has been spurred by research that led to increasing knowledge of the causes, timing, sequence, and frequency of the genetic, molecular, and cellular changes that drive cancer initiation and development.

Increasing Options for Colorectal Cancer Screening

Colorectal cancer screening has helped reduce U.S. colorectal cancer incidence and mortality rates because it can identify precancerous colorectal abnormalities, which can be removed before they have a chance to develop into cancer, as well as early-stage cancers, which are more easily treated compared with advanced-stage cancers (see sidebar on **Consensus Among Cancer Screening Recommendations**, p. 42) (113). However, colorectal cancer remains the fourth most commonly diagnosed cancer and the second leading cause of cancer-related deaths (3).

One in every three U.S. adults for whom colorectal cancer screening is recommended is not up to date with screening (113). It is clear that new ways to increase participation in colorectal cancer screening could significantly reduce the burden of this common cancer.

Research shows that people who are able to pick the colorectal cancer screening test they prefer are more likely to actually get the test done (115).

In an effort to increase the number of colorectal cancer screening options, and hopefully thereby increase the number of people who are screened, researchers built on the discovery that a specific epigenetic abnormality—

FIGURE 10 GENOMICALLY INFORMED CLINICAL TRIALS

One of the major uses of genomics in clinical research is in the design and execution of novel 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) in lung cancer.

Figure adapted from Ref. (1)

BEATING CHILDHOOD LEUKEMIA THANKS TO RESEARCH

A MESSAGE FROM TONYA AND JOHN THEODOSIADES, LUKE'S PARENTS

LUKE THEODOSIADES // AGE 13 // SWARTHMORE, PENNSYLVANIA

Our son Luke was diagnosed with acute lymphoblastic leukemia (ALL) in June 2015. The leukemia did not respond to chemotherapy, so his doctors turned to research to look for a way forward. The researchers found a chromosomal translocation in the leukemia cells that suggested the drug ruxolitinib (Jakafi) might help. It did. After 9 months of chemotherapy and ruxolitinib, there was no sign of leukemia cells with the chromosomal translocation. But there were some other leukemia cells there. After CAR T-cell therapy, these cells were also undetectable, but the doctors are worried that Luke will relapse, and so he is having a bone marrow transplant at the end of August 2016. We hope that this will put Luke's cancer behind him, and he will be back playing baseball next season.

Luke's diagnosis with ALL came just days after we took him to the pediatrician for what we thought was sports-induced asthma. He had just finished sixth grade and was playing baseball every day. It was hot out, and when he seemed to be having breathing issues while playing and was sleeping a lot when he came home, we weren't too worried. But after about a week, we took him to the pediatrician to find out what was going on.

After weighing Luke and discovering he had lost about 10 pounds, the pediatrician began asking lots of questions and ordered blood work and a chest X-ray. She called the next afternoon and said, "I hate to tell you this, but Luke has leukemia, you need to go to Children's Hospital of Philadelphia right away."

The doctors were waiting for us and immediately started leukopheresis. There were so many white cells in Luke's blood that they had to take some out. They could not believe that he had spent the day at the pool and playing baseball. They told us that with a white blood cell count as high as his, he should have been unable to get out of bed.

Luke spent the next 5 weeks in the hospital receiving intensive chemotherapy. But the leukemia didn't fully respond to treatment. When the doctors suggested having his leukemia cells analyzed by researchers, we were happy to agree because we wanted solutions to the problem and a cure for Luke.

The research analysis identified a chromosomal translocation, GOLGA5-JAK2, which led the doctors to add a drug called ruxolitinib to Luke's chemotherapy. After about 9 months, leukemia cells with the GOLGA5-JAK2 translocation were undetectable. But there were other leukemia cells still there.

Fortunately, early on in Luke's treatment, the doctors had taken his T cells because they were hoping that he would eventually be a candidate for a CAR T-cell therapy clinical trial. The ruxolitinib/chemotherapy combination did the job. This treatment knocked down the number of leukemia cells sufficiently so that Luke could enroll in the trial.

Luke received the CAR T-cell therapy in May 2016. The procedure was very simple, and he had no side effects.

A few weeks later, we learned that there were no leukemia cells detectable at all.

The doctors are worried that because Luke's leukemia was very aggressive and chemoresistant, the CAR T-cell therapy will not keep him in remission long term, so he is scheduled to have a bone marrow transplant at the end of August.

The whole procedure will be tough for Luke because he will have to be in the hospital for up to 8 weeks, and after that, he won't be able to go back to school for another 6 or 9 months. Luke loves being in school with his friends, as he is very sociable. Throughout his treatment, we have tried to keep things as normal as possible for Luke and his brothers. He has been to school and has played baseball as much as he can. These activities seem to have really helped him deal with everything he has been through.

We are very fortunate to have had incredible support from our family and the community throughout this experience. Our lives were changed forever, but we hope to give back by telling how research changed our lives by giving us options for Luke. With more funding, research can do even more; maybe it can lead to a cure for everybody.

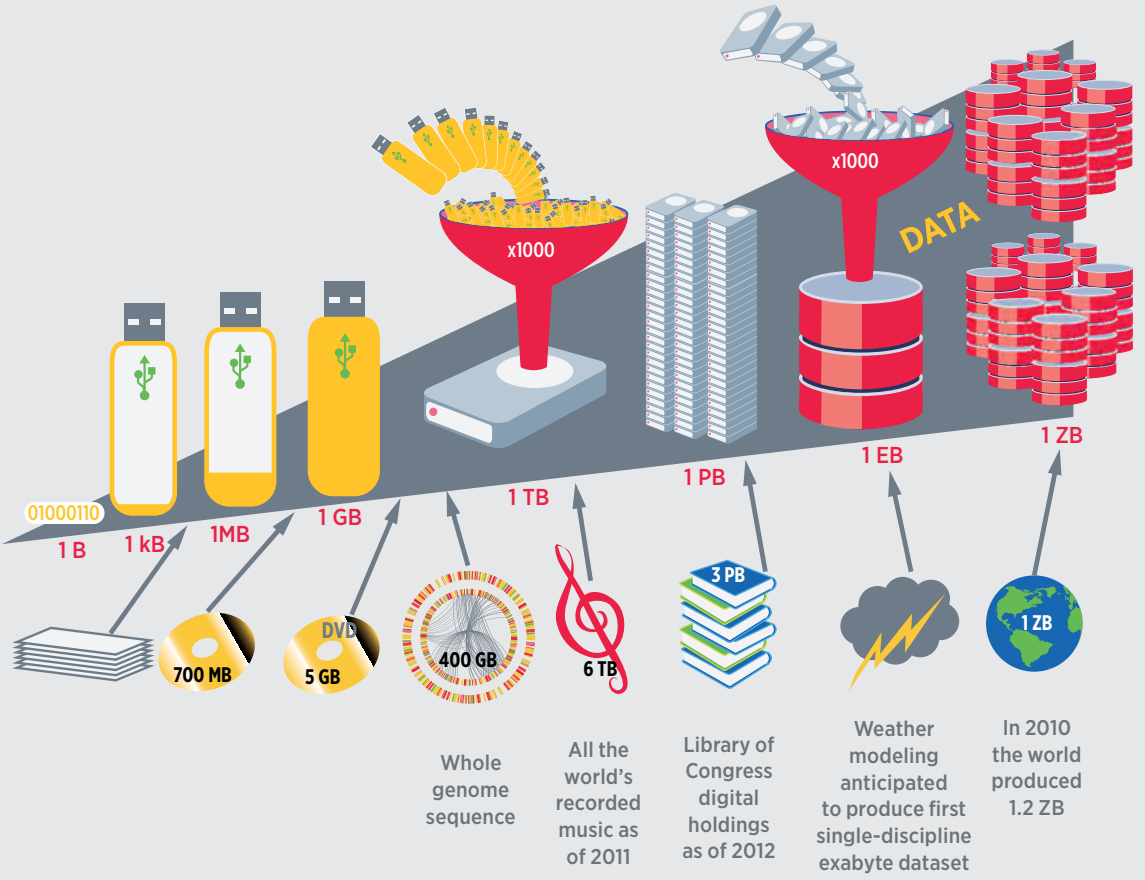
ACUTE LYMPHOBLASTIC LEUKEMIA IS THE MOST COMMONLY DIAGNOSED CANCER AMONG U.S. CHILDREN

© Vera LaMarche

"With more funding, research can do even more; maybe it can lead to a cure for everybody."

FIGURE 11

HOW BIG IS BIG?



Data of any kind are measured in bytes. A byte is eight binary digits (01000110) and is recognized by a computer as a single character. One thousand bytes make up a kilobyte (kB); the average Word document (white pages) is tens to hundreds of kB. The average compact disc can hold 700,000 kB, which is 700 megabytes (MB), of data (gold disc). A thousand MB are contained within a gigabyte (GB), illustrated by the thumb drive, and the average digital video disc (DVD) holds nearly 5 GB of data (gold DVD). It would take more than 80 DVDs to store the data from sequencing an individual's entire genome (the Circos plot), which is approximately 400 GB. A 2011 McKinsey/MGI report estimated that all of the world's recorded music up to that year could be stored in 6 terabytes (TB; music note); it would take 6,000 1-GB thumb drives to store all of these data (107). As of April 25, 2012, the Library of Congress's digital holdings collection contained 3 petabytes (PB; stack of books) of data, which is 3,000 TB or 3 million 1-GB thumb drives (108). Researchers at the Lawrence Berkeley National Laboratory estimate that within the next few years, it will generate more than an exabyte (EB; cloud) of data modeling the weather. It would take more than 1 billion 1-GB thumb drives to store these data (109). It is estimated that in 2010, the world collectively created more than 1.2 zettabytes (ZB; globe) of data (110). Big data sets are unique in that they are too large to be stored and analyzed using traditional relational methodologies. The complexity of cancer and its treatment is creating big data sets, and the field and the patients it serves will benefit greatly from research into big data systems, methodologies, and solutions.

Figure adapted from Ref. (1)

the presence in blood of epigenetic marks called methyl groups on part of a gene called Septin-9—is associated with colorectal cancer to develop a blood-based test (116). The new test, Epi proColon, detects the Septin-9 epigenetic abnormality in blood, and it was approved by the FDA for screening those who choose not to be screened by colonoscopy or a standard stool-based test in April 2016. Although further research is needed to determine the long-term benefits of Epi proColon, including whether or not it will help increase the number of people who are screened for colorectal cancer, this approval exemplifies how researchers translate scientific discoveries to new FDA-approved medical products.

Treatment With Surgery, Radiotherapy, and Cytotoxic Chemotherapy

The discovery that most cancers arise as a result of the accumulation of genetic mutations within cells (see **Cancer Development: Influences Inside the Cell**, p. 18), coupled with advances in biology, chemistry, physics, and technology, sets the stage for the new era of precision medicine.

Precision medicine is broadly defined as treating a patient based on characteristics that distinguish that individual from other patients with the same disease (see **Figure 2**, p. 22) (25). As we have learned more about 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. This is changing the standard of care for many patients 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.

The molecularly targeted therapeutics that are the foundation of precision medicine tend to be more effective and less toxic than two of the long-standing pillars of cancer treatment—radiotherapy and cytotoxic chemotherapy (see **Figure 12**, p. 62). 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. Whatever the reason, the reality is that these therapeutic modalities form the foundation of treatment for almost all patients with cancer, including those for whom molecularly targeted therapeutics and other novel anticancer agents are appropriate.

About
50%
of all U.S. cancer patients have radiotherapy to shrink or eliminate tumors or to prevent local recurrence (118).

In the United States, colorectal cancer screening:

has helped dramatically reduce colorectal cancer incidence and mortality (113);

is not used by one in three people for whom it is recommended (113); and

could save 1,000 additional lives each year if the proportion of individuals following the colorectal cancer screening recommendations increased to 70.5% (114).

For many patients with cancer, surgery is a foundation of their treatment plan. 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. In the early 1990s, surgeons began performing minimally invasive laparoscopic surgery for some types of cancer. Subsequently, laparoscopic surgery for some types of cancer was modified to include a computer console that the surgeon uses to manipulate robotic arms attached to the surgical instruments. However, there have been few studies comparing the effectiveness of different forms of surgery

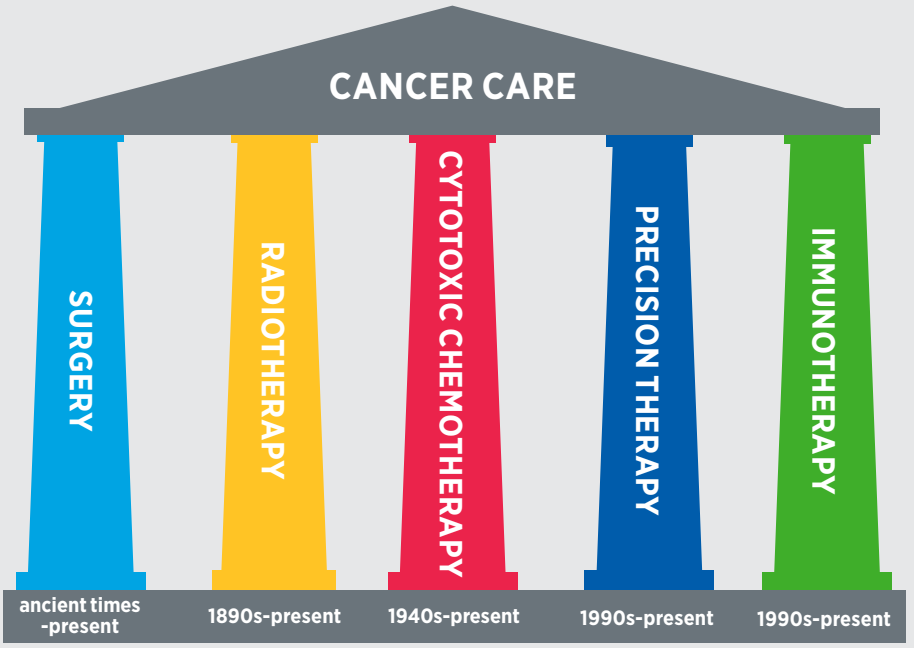
(118). One randomized clinical trial showed no difference in disease-free and overall survival among patients with colorectal cancer who had laparoscopic surgery or open surgery (119), while a recent study that looked back at outcomes for patients who underwent robot-assisted laparoscopic prostatectomy or open radical prostatectomy for nonmetastatic prostate cancer found that the robotic surgery yielded a number of benefits (120). On the other hand, early results from a randomized, controlled phase III trial comparing these two approaches showed there were no significant differences in intra- and postoperative outcomes (121). Thus, more research is needed to more fully compare the effectiveness of different types of surgery, robotic surgery in particular, which typically costs more than laparoscopic or open surgery, for all types of cancer (118).

In 2011, more than
300,000
robotic surgeries were performed in the United States, compared with fewer than 60,000 in the rest of the world (122).

The shift from open surgery to minimally invasive laparoscopic surgery for certain types of cancer is not the only surgical advance that has been made to reduce adverse effects that can accompany surgery. One recent advance was to reduce the use of axillary lymph node dissection, an invasive surgical procedure in which large numbers of lymph nodes in the armpit are removed, in the treatment of breast cancer. Up to 40 percent of patients with breast cancer who have an axillary lymph node dissection have been reported to experience lymphedema, swelling of the arm that can limit movement (123). One concern about reducing the use of axillary lymph node dissection was that it might negatively affect outcomes for patients. However, a recent study showed that women with breast cancer that had spread to one or two lymph nodes who

FIGURE 12

MORE OPTIONS FOR CANCER CARE



Physicians often refer to the "pillars" of cancer treatment. For thousands of years, there was only one treatment pillar: surgery. In 1896, a second pillar, radiotherapy, was added (117). The foundations for the third treatment pillar, cytotoxic chemotherapy, were laid in the early 1940s when a derivative of nitrogen mustard was explored as a treatment for lymphoma. These three pillars—surgery, radiotherapy, and cytotoxic chemotherapy—continue to be 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 Ref. (24)

were treated with lumpectomy, radiotherapy, and systemic therapy had equally good disease-free and overall survival after 10 years whether or not they had an axillary lymph node dissection (124).

Picturing Cancer More Clearly

The more precise a patient's diagnosis, the more easily the patient's physicians can tailor his or her treatment to ensure that it is as effective and innocuous as possible. Among the tools physicians use to make cancer diagnoses is positron emission tomography–computed tomography (PET–CT or PET), a form of imaging that can help physicians precisely locate the position of a patient's cancer within his or her body and determine the extent to which the cancer may have spread.

Before having a PET scan, patients are injected with a radioactive imaging agent. The PET scan detects where in the body the radioactive agent accumulates. In June 2016, the FDA approved a new kit called Netspot for preparing the injectable radioactive imaging agent gallium (Ga) 68 DOTATATE for use with PET to locate neuroendocrine tumors with the protein somatostatin receptor on the surface. Ga 68 DOTATATE locates these tumors because it is analogous to somatostatin, which naturally attaches to the somatostatin receptor.

Neuroendocrine tumors

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

PET imaging using Ga 68 DOTATATE has been shown to more precisely locate somatostatin receptor–positive neuroendocrine tumors compared with previous approaches, which has the potential to affect patient treatment in a number of ways (125). For example, it can better identify disease sites for potentially curative surgery or determine if a patient has metastases that cannot be removed by surgery such that he or she requires additional treatment approaches. It also reduces radiation exposure for patients compared with an imaging agent that has been used for the past few decades (indium-111 radiolabeled octreotide) (125).

In clinical cancer care, PET imaging is not only used to help identify cancer initially, but also to monitor patients for potential disease recurrence. In May 2016, the FDA approved the radioactive imaging agent fluciclovine fluorine (F) 18 (Axumin) for use with PET to screen men whose prostate cancer was suspected to have recurred based on elevated prostate specific antigen (PSA) levels after previous successful treatment. Fluciclovine F 18 comprises an F 18 radiolabeled synthetic amino acid (a building block of proteins) that is preferentially taken up by many types of cancer cells, including prostate cancer cells, compared with surrounding normal tissues.

Recurrent prostate cancer is usually detected by a rise in PSA levels; however, the location and extent of the disease cannot always be detected using currently available imaging tools. In a recent small study in which men with suspected prostate cancer recurrence underwent PET imaging with fluciclovine F 18 and PET imaging with the currently used radioactive imaging agent choline C 11, fluciclovine F 18 located sites of prostate cancer recurrence in more men (126). Precisely locating sites of prostate cancer recurrence is important for physicians as they tailor a man's next treatments. For example, a single site of recurrence might be treatable with local therapy, such as surgery or radiotherapy, whereas multiple sites of recurrence might require systemic treatment, such as antihormone therapy or chemotherapy.

Tailoring Treatments to Reduce Adverse Effects

Radiotherapy and cytotoxic chemotherapy are mainstays of cancer care (see sidebar on **Using Radiation in Cancer Care**, p. 64). However, both types of treatment can have long-term adverse effects on patients. Thus, physicians are looking to tailor each patient's treatment to be only as aggressive as is necessary for it to be effective. They are doing so 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.

Many patients with early-stage breast cancer are treated with breast-conserving surgery followed by whole breast radiotherapy. For several decades, the radiotherapy portion of this treatment regimen has comprised 5 to 7 weeks of daily radiotherapy. A few years ago, long-term follow-up from several clinical trials showed that hypofractionated radiotherapy, whereby patients receive fewer but higher doses of radiotherapy over a shorter time period, was as effective as the traditional course of radiotherapy at preventing local breast cancer recurrence (127, 128). New

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

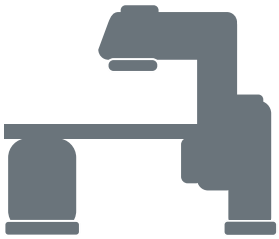
RADIOTHERAPY

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.

It works chiefly by damaging DNA, leading to cell death.

TYPES OF RADIOTHERAPY

EXTERNAL BEAM RADIOTHERAPY directs radiation at the tumor from outside the body; it is the most common form of radiotherapy. Standard linear accelerators use electromagnetic fields to accelerate electrons, which can be used directly or collided with a metal target to generate high-energy X-rays. Electrons and photons (X-rays) are the most common sources of radiation in external beam radiotherapy.



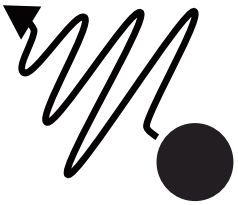
Conventional (2-D) external beam radiation therapy delivers a high-energy X-ray beam from one or multiple directions. Imaging of the treatment area is typically performed using low-energy diagnostic X-rays. It is chiefly used in settings where high precision is not required, such as in the treatment of bone metastases.

3-D conformational radiotherapy (3DCRT) uses specialized imaging, usually computed tomography (CT) and/or magnetic resonance imaging (MRI) and planning software, to deliver high-energy X-rays via multiple beams that more precisely fit the shape and size of the tumor.

Intensity-modulated radiotherapy (IMRT) is a further refinement of 3DCRT that more precisely focuses and shapes the radiation by dividing each beam into many "beamlets," each of which can have a different intensity. IMRT is particularly useful when a sharp dose gradient is required between the tumor and sensitive tissues, for example, the optic nerves.

Intraoperative radiation therapy uses electron beam (superficial) radiation directly on tumors that have been exposed during surgical procedures.

Stereotactic radiotherapy is used in both stereotactic surgery (SRS) and stereotactic body radiotherapy (SBRT). It uses many (typically more than eight) beams with a highly sophisticated imaging system to direct radiation to very well-defined smaller tumors. Typically, SRS is used to treat tumors of the brain and central nervous system, whereas SBRT can be used on small tumors within larger organs of the body.



PARTICLE THERAPY uses protons or carbon ions rather than X-rays as the source of energy. In contrast to X-rays that pass through 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.

Adapted from (24)

USES OF RADIOTHERAPY

Radiotherapy is often used serially with surgery, chemotherapy, and/or immunotherapy to control or eliminate cancer.

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.

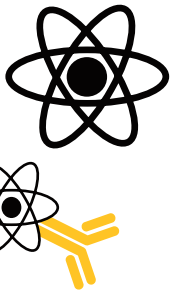
PALLIATIVE radiotherapy is used to reduce or control symptoms of disease when cure by another method is not possible.

TYPES OF RADIOTHERAPY

BRACHYTHERAPY places small radioactive sources in or next to the tumor. There are two forms of brachytherapy.

Permanent implantation inserts radioactive sources into the tumor; (e.g., placement directly into the prostate for the treatment of prostate cancer or into the tumor vasculature; see radioembolization below).

Temporary placement of radioactive sources. In one form of this treatment, moderately active sources are placed for 1 to 4 days (e.g., in the treatment of soft-tissue sarcoma). In "high dose–rate" brachytherapy, a highly active source is inserted for a few minutes (e.g., in the curative treatment of cervical cancer).

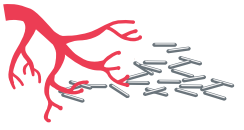


RADIOISOTOPE Systemic ingestion or infusion of radioisotopes, which are natural or synthetic variations of elements that are unstable and emit high-energy rays as they stabilize, or radiolabeled therapeutics such as a therapeutic antibody. For example, the use of iodine-131 to treat thyroid cancer or yttrium-90 ibritumomab (Zevalin) to treat non-Hodgkin lymphoma, respectively.

INTERVENTIONAL RADIOLOGY

INTERVENTIONAL RADIOLOGY combines imaging with minimally invasive techniques designed to treat cancer locally.

Chemoembolization is a process by which therapeutic-coated particles are injected directly into the tumor vasculature in order to prevent blood flow and increase the therapeutic concentration to very high levels.

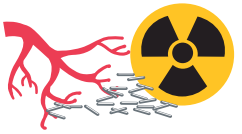


Cryoablation is a technique wherein needles are directly inserted into the tumor and cooled to very cold temperatures, causing tumor cell death.

High-intensity focused ultrasound applies high-intensity focused ultrasound waves to locally heat and destroy tumors.

Microwave ablation uses microwave radiation to locally heat and destroy tumors.

Radioembolization is the injection of radioactive microspheres directly into the tumor vasculature (e.g., injection of yttrium-90 microspheres into a liver tumor via the hepatic artery).



Radiofrequency ablation is a technique wherein needles are directly inserted into the tumor and an electrical current is used to heat the needle, causing tumor cell death.

research shows that hypofractionated radiotherapy also significantly reduces adverse treatment effects compared with the traditional course of radiotherapy (129, 130).

Compared with a traditional course of radiotherapy, hypofractionated radiotherapy requires fewer visits to the radiation oncologist, which could help lower health care costs and increase convenience for patients (131). However, few U.S. patients with breast cancer for whom hypofractionated radiotherapy would be a suitable option currently receive the treatment. Researchers hope that the new data showing a reduction in adverse effects will help increase the number of women who have their radiotherapy tailored to be as effective yet innocuous as possible.

One approach that researchers are using to reduce the adverse effects of chemotherapy is to develop nanotechnology-based forms of cytotoxic chemotherapeutics. These allow the delivery of higher levels of cytotoxic chemotherapeutics to cancer cells than the usual forms of the anticancer agents, thereby increasing effectiveness while reducing adverse effects.

In October 2015, the FDA approved a nanotechnology-based form of the cytotoxic chemotherapeutic irinotecan, which is used in the conventional form to treat some patients with several types of cancer, including colorectal, lung, and ovarian cancers. The new nanotechnology-based anticancer agent, irinotecan liposome injection (Onivyde), can now be used in combination with two other cytotoxic chemotherapeutics, fluorouracil and folinic acid (leucovorin), for treating patients with advanced pancreatic cancer that has progressed despite treatment with gemcitabine-based chemotherapy. The decision was made after results from a large clinical trial showed that patients lived significantly longer when irinotecan liposome injection was added to fluorouracil and folinic acid (132).

Nanodrugs

are 20,000 times smaller than the smallest width of a human hair, comprise an anticancer agent and a nanosized carrier that selectively delivers the drug to the cancer cells and protects the drug from being destroyed by the body, and increase efficacy of the anticancer agent while reducing adverse effects.

2%:

the 5-year relative survival rate for patients with advanced pancreatic cancer (9).

Increasing Options for Patients With Soft Tissue Sarcoma

Soft tissue sarcoma is a relatively rare type of cancer, with 12,310 U.S. adults expected to be diagnosed with the disease in 2016 (3). It is actually not one type of cancer, but instead is 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. Two of the most common types of adult soft tissue sarcomas are liposarcoma and leiomyosarcoma. Liposarcomas arise in fat cells in any part of the body, but most commonly fat cells in the muscles of the limbs or in the abdomen. Leiomyosarcomas arise in smooth muscle cells, most frequently those in the uterus or abdomen.

Patients with advanced soft tissue sarcoma have a poor prognosis; median survival is estimated to be just 12 to 15 months (133). Those for whom surgery is not a possibility are usually treated with various combinations of cytotoxic chemotherapeutics to control the growth of the tumor, but no chemotherapy treatments have been shown to improve survival, and options are limited.

This situation changed recently, when results from a large-scale clinical trial showed that the cytotoxic chemotherapeutic eribulin mesylate (Halaven) significantly improved survival for certain patients with liposarcoma compared with the cytotoxic chemotherapeutic dacarbazine (134). These results led the FDA to approve eribulin mesylate for patients with liposarcoma that cannot be removed by surgery or that is advanced and that has progressed despite treatment with a chemotherapy regimen that includes a type of cytotoxic chemotherapeutic called an anthracycline—for example, doxorubicin—in January 2016. With eribulin mesylate having previously been approved for treating metastatic breast cancer, this new approval both expands the number of patients who may benefit from the cytotoxic chemotherapeutic and increases the return on prior investments in biomedical research.

In October 2015, the FDA added another cytotoxic chemotherapeutic to the armamentarium for physicians treating patients with soft tissue sarcomas when it approved trabectedin (Yondelis) for treating some liposarcomas and leiomyosarcomas. The decision was based on the fact that trabectedin extended the average time before disease

Eribulin mesylate is a synthetically produced version of a natural product isolated from the marine sponge *Halichondria okadai* and **trabectedin** is a modified version of a natural product from the sea squirt *Ecteinascidia turbinata*, highlighting the utility of natural products research.

progressed compared with dacarbazine for patients whose tumors could not be surgically removed or had advanced disease and who had been previously treated with an anthracycline-containing chemotherapy regimen (133). This approval is providing new hope to patients like **Nancy McGuire** (see p. 68).

Working Together to Treat Colorectal Cancer

Although screening for colorectal cancer has helped lower U.S. colorectal cancer incidence and mortality rates (113) (see **Increasing Options for Colorectal Cancer Screening**, p. 57), the disease remains the second leading cause of cancer-related death in the United States (3). In September 2015, the FDA provided fresh hope for patients with the disease when it approved a new treatment option for advanced colorectal cancer that is no longer responding to other treatments: a combination of drugs formulated together in a single tablet called Lonsurf (previously known as TAS-102).

The two therapeutics in TAS-102—trifluridine and tipiracil—work together to target colorectal cancer. Trifluridine is a cytotoxic chemotherapeutic that causes damage to DNA in the rapidly multiplying cancer cells, which can ultimately trigger cell death; tipiracil prevents rapid breakdown of trifluridine, thereby maintaining adequate levels of trifluridine in the body.

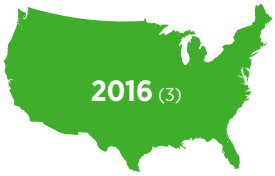
Trifluridine damages DNA in a similar way to the cytotoxic chemotherapeutic fluorouracil, which has been used as a treatment for colorectal cancer for decades. However, in the phase III clinical trial that led to the FDA approval of TAS-102, the new combination chemotherapy tablet improved survival compared with placebo even for those patients who had colorectal cancer that was no longer responding to treatment with fluorouracil-containing chemotherapy regimens (135).

Treatment With Molecularly Targeted Therapeutics

Research is powering the field of precision medicine in many ways, including by increasing our understanding of the genetic, molecular, and cellular changes that lead to cancer initiation and development. Therapeutics directed to the molecules involved in different stages of the cancer process target the cells within a tumor more precisely than cytotoxic chemotherapeutics. 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.

Estimated New Colorectal Cancer Cases

134,490



49,190

1,477,402

752,731

Estimated New Colorectal Cancer Deaths

BEATING LEIOMYOSARCOMA THANKS TO SURGERY, RADIOTHERAPY, AND CHEMOTHERAPY

NANCY MCGUIRE // AGE 70 // GREAT FALLS, VIRGINIA

LEIOMYOSARCOMA IS A TYPE OF SOFT TISSUE SARCOMA

After I was diagnosed with leiomyosarcoma, it was very hard to find a medical oncologist who specialized in treating sarcoma. Eventually, my daughter found someone at the University of Pennsylvania, which is close to her home. He has guided me through numerous treatments over the past 6 ½ years, including, most recently, a new chemotherapy called trabectedin (Yondelis). It has worked so well that I've been given a vacation from treatment. For now, I feel wonderful, emotionally and physically. Life is good.

In December 2009, just after a few days of having pain in my lower pelvic area that wouldn't go away, I went to my primary care physician who ordered a CT scan and MRI for that very day. The tests showed a mass of some description in my lower pelvic area, so I had surgery 17 days later, not knowing exactly what it was.

When I came out of surgery, the doctors had already told my husband and family that I had cancer and that pathology would determine what type. My diagnosis was leiomyosarcoma. I was devastated. I couldn't do anything. After I came home from the hospital, all I could do was stare out the window. I was convinced that I would die within months.

My husband, children, sister, and church friends were a huge support, and I was eventually able to come to terms with my diagnosis.

After the surgery, I saw a local radiologist and had 28 radiation treatments. When she told me that she saw about one person a year who had leiomyosarcoma, I realized how hard it would be to find an expert in treating this disease in my area.

My daughter, who lives in the suburbs of Philadelphia, found a sarcoma specialist at the University of Pennsylvania, Dr. Arthur Staddon. The first time I saw him, he told me the disease was not curable but that it was certainly treatable. It was the first time I had felt optimistic about my future since my diagnosis.

Over the years, I have received many different treatments. Initially, I had CT scans every 3 months, and Dr. Staddon monitored the disease. After about a year, tumors in my liver appeared, and I had a course of chemotherapy, gemcitabine (Gemzar), and docetxel (Taxotere), and then surgery to remove tumors from my liver, some of which had been killed as a result of the chemotherapy.

These treatments were followed by another period of monitoring my disease with CT scans, which eventually showed further growth of tumors in my left lung. I started a course of chemotherapy with doxorubicin (Adriamycin). Following that treatment, I had surgery. After a year or so, I had another major lung surgery to remove numerous tumors in my right lung. Four months later, I had cryoablation, microwave ablation, and chemoembolization to destroy tumors in my liver.

In January 2016, I started taking trabectedin, right after it had been approved by the FDA. After just three treatments, a CT scan showed there were no new tumors, and the existing tumors had shrunk. Three more treatments later, the scan revealed more significant improvement, including showing that some tumors had decreased in size even further. Because my most recent CT scan indicated additional improvement, Dr. Staddon recommended I stop taking trabectedin for a while. I will have another scan in September [2016]. Depending on what that shows, we will make a decision about whether to restart treatment with trabectedin or continue without treatment.

One great thing about the trabectedin treatment is that I was able to receive the 24-hour infusion at my daughter's home, rather than receiving it in the hospital. It is so much more pleasant to go through the chemotherapy infusion in a familiar environment with my family around me. It helped me keep a positive attitude, which makes a big difference to me.

I am really grateful for all the treatments that have kept me alive for the past 6 ½ years. The goal of a patient with cancer is to live long enough to be around when the next new drug is developed. The only way that is going to happen is with further research and the funding that supports it.

© Nor Idoksal

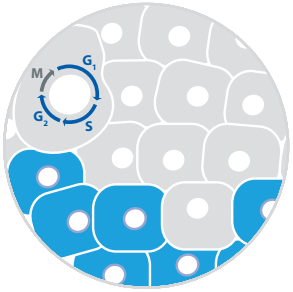

“It [trabectedin] has worked so well that I’ve been given a vacation from treatment.”

Helping Some Lung Cancer Patients Breathe Easier

Research has spurred tremendous progress against lung cancer in recent years through the identification of the genetic, molecular, and cellular changes that fuel cancer growth in certain patients and the development of therapeutics that target these changes. Unfortunately, the majority of lung cancers that initially respond to the new molecularly targeted therapeutics eventually progress and are said to have become treatment resistant (see sidebar on **The Challenge of Treatment Resistance**).

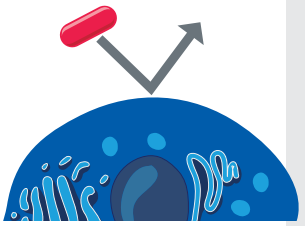
THE CHALLENGE OF TREATMENT RESISTANCE

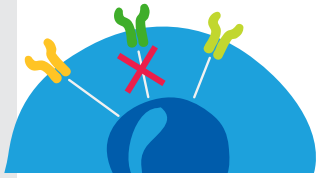
Diversity, or heterogeneity, among cancer cells within and between tumors is ultimately what leads to treatment resistance. Some examples of heterogeneity are as follows:



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

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





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

Adapted from (1)

Two FDA decisions in late 2015 have helped address the problem of treatment resistance for two groups of patients with non–small cell lung cancer (NSCLC)—the most commonly diagnosed form of lung cancer in the United States (3).

In November 2015, the FDA approved a molecularly targeted therapeutic called osimertinib (Tagrisso) for patients with NSCLC that has become resistant to other therapeutics that target the same molecule, EGFR. At the same time, the FDA approved a new test, or companion diagnostic, to identify the patients for whom osimertinib is approved, the cobas EGFR Mutation Test v2 (see sidebar on **Companion Diagnostics**, p. 71).

About 10 to 20 percent of patients with NSCLC have tumors that are fueled by mutations in the EGFR gene (136), and the FDA has previously approved three EGFR-targeted therapeutics, afatinib (Gilotrif), erlotinib (Tarceva), and gefitinib (Iressa), for treating these patients. Although most NSCLCs fueled by EGFR mutations respond to afatinib, erlotinib, and gefitinib, not all do, and even those that do respond initially eventually become resistant to these EGFR-targeted therapeutics (136). The most frequent cause of resistance is the acquisition by some cells in the tumor of a new mutation in the EGFR gene called the EGFR T790M mutation.

Osimertinib specifically targets cancer-driving mutant forms of EGFR, including that produced by the EGFR T790M mutation. It is the only FDA-approved therapeutic that can target NSCLCs with this mutation, providing new hope for patients like **Ginger Tam** (see p. 72). In phase II clinical trials, osimertinib treatment led to tumor shrinkage or disappearance in patients with NSCLC fueled by the EGFR T790M mutation (137), and it is hoped that future studies will reveal that the molecularly targeted therapeutic also extends survival for these patients.

In December 2015, the FDA approved a molecularly targeted therapeutic called alectinib (Alecensa) for treating patients with NSCLC that harbors mutations in the ALK gene and who are not responding to the ALK-targeted therapeutic crizotinib (Xalkori), which was FDA approved for treating this group of patients in August 2011.

Lung cancer
remains the leading cause of cancer-related death both in the United States and worldwide (8).

ALK gene mutations fuel 3 to 7 percent of NSCLCs (138). Although crizotinib benefits many patients with NSCLC driven by ALK, not all patients respond. Moreover, the majority of patients who initially respond to crizotinib treatment eventually relapse because the cancer becomes resistant to the ALK-targeted therapeutic (138).

One cause of crizotinib resistance is the emergence of new mutations in ALK. Alectinib is able to block many of the unique forms of ALK that result from these new mutations and in phase I/II clinical trials, treatment with alectinib caused tumor shrinkage or disappearance in patients with crizotinib-resistant NSCLC driven by ALK. Alectinib was even able to shrink tumors that had metastasized to the brain, which is something the other ALK-targeted therapeutics are less able to do (138). It is hoped that future studies will show that alectinib also improves survival for patients with ALK-fueled NSCLC.

About 1 percent of patients with NSCLC have tumors that are fueled by mutations in the ROS1 gene, which generates a protein that is related to ALK (139). In March 2016, the FDA approved crizotinib for treating patients with ROS1-fueled NSCLC after a phase I clinical trial showed that the anticancer therapeutic caused partial or complete tumor shrinkage in patients with this type of NSCLC (139). This new approval both expands the number of patients with NSCLC who may benefit from crizotinib and increases the return on prior investments in biomedical research.

Most patients with EGFR-mutant NSCLC have the nonsquamous cell type of NSCLC (140). Even though EGFR mutations are rarely detected in the less common squamous cell type of NSCLC, most of these cancers have elevated levels of EGFR protein on their surface (140). This observation suggested to researchers that EGFR-targeted therapeutics might benefit patients with squamous NSCLC.

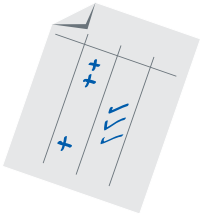
Three

ALK-targeted therapeutics have been approved by the FDA for patients with ALK mutation–fueled NSCLC: crizotinib, ceritinib, and alectinib.

COMPANION DIAGNOSTICS

The effective therapeutic use of precision medicines 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)

SURVIVING LUNG CANCER THANKS TO CLINICAL TRIALS

GINGER TAM // AGE 54 // NORTHFIELD, ILLINOIS

Since I was diagnosed with metastatic lung cancer in 2011, I have received numerous treatments, most by participating in clinical trials. A lot of these treatments have caused me to lose my voice, which was devastating to me because I am a professional singer. Within 2 months of starting a clinical trial testing a drug called osimertinib (Tagrisso), I had my voice back, along with my breath. Although my lung cancer progressed after 2 years of receiving osimertinib, my experience with the drug was so awesome that I always said if my lung cancer progressed again, I would look to enroll in a clinical trial testing osimertinib in combination with other treatments. Today I am at that point. I am enrolling in a clinical trial of osimertinib plus another treatment. I am thrilled.

My journey with lung cancer started 5 ½ years ago, when I was just 49. I went to the doctor due to a persistent cold and cough that had not gone away despite several courses of antibiotics. The doctor ordered a chest X-ray, and after taking one look at the film she said, "It looks like it is metastatic lung cancer and there's just so much of it," then left me alone in the exam room.

All I could think about was: What would happen to my 8-year-old daughter? I was a single mom and everything I had heard about lung cancer pointed to death.

My fears were compounded when, after a biopsy showed that I had non–small cell lung cancer, the doctor told me I had maybe 2 years left to live at the most.

I wanted more. So I sought a second opinion at a research hospital, Rush University Medical Center, in Chicago. The doctors there would not give me a timeline saying that there were lots of new drugs in development, and they could not give me an accurate prognosis.

That made me confident in the treatment plan that they outlined, and I started chemotherapy almost immediately. It didn't work, however, and the lung cancer continued to progress.

The doctors started me on erlotinib (Tarceva), which is an EGFR inhibitor, even though my diagnostic biopsy had not been tested for EFGR mutations. They had a hunch that it might work because I was so young, and EGFR mutations are more common among younger people. It did work. In fact, I had almost a complete response.

Unfortunately, it didn't last, and the cancer progressed again. This time they did a biopsy and tested it for a specific EGFR mutation, the EGFR T790M mutation, which is a frequent cause of resistance to EGFR inhibitors in lung cancer.

My doctor helped me find an early-stage clinical trial of a drug called CO-1686, which was designed to inhibit the EGFR T790M mutation. It didn't work for me, so I had to start a really strong chemotherapy combination, carboplatin-taxol. It was extremely tough. It made me so sick. I still have neuropathy in my feet as a result of the chemo.

After my lung cancer progressed again, I went back to erlotinib. This kept my lung cancer at bay for 6 months, at which point I was able to get the last spot in Denver in a clinical trial testing osimertinib, another drug designed to inhibit the EGFR T790M mutation.

The 2 years I spent taking osimertinib were so different from the rest of my time being treated for lung cancer. I felt healthier than I had in a long time. There were almost no side effects, my voice came back, I could sing again, I could exercise, and I took my daughter to Paris where we did bike tours and walked everywhere. It was awesome.

In early 2016, I had to switch to another clinical trial because my lung cancer progressed again. This trial was testing an antibody-drug conjugate. The drug gave me fewer side effects than regular chemotherapy, but my quality of life was not as good as it was when I was taking osimertinib. However, my time in this trial has come to an end and I am so very happy to be returning to an osimertinib trial.

Thank God for clinical trials. I am alive 5 ½ years after my diagnosis with metastatic lung cancer. Statistics said I should have been gone years ago, but I'm not. I'm still here. I'm with my daughter, and that is what matters.

LUNG CANCER IS THE LEADING CAUSE OF CANCER-RELATED DEATH IN THE UNITED STATES

© Jimmy Fishbein

> Within two months of starting a clinical trial testing a drug called osimertinib (Tagrisso), I had my voice back.

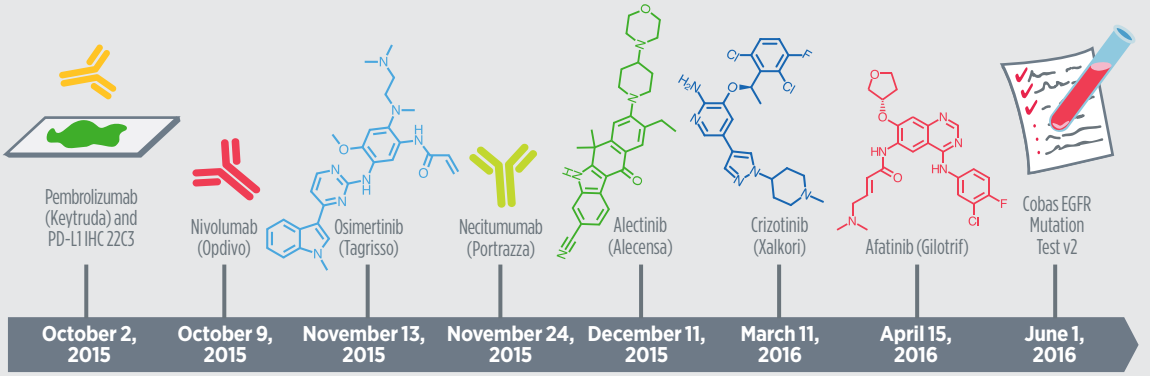
In fact, phase III clinical trials showed that two different EGFR-targeted therapeutics, afatinib and necitumumab (Portrazza), improved survival for patients with advanced squamous NSCLC (140, 141). These two molecularly targeted therapeutics were approved by the FDA in April 2016 and November 2015, respectively. Of note, afatinib is approved as a stand-alone treatment for patients whose disease has progressed despite treatment with a platinum-based cytotoxic chemotherapeutic. Necitumumab is approved for use in combination with the cytotoxic chemotherapeutics gemcitabine and cisplatin for treating patients who have not previously received medication specifically for their advanced squamous NSCLC.

Progress against lung cancer in the 12 months from Aug. 1, 2015 to July 31, 2016, is not limited to the five molecularly targeted therapeutic FDA approvals highlighted here (see **Figure 13**). During this period, the FDA also approved two immunotherapeutics for treating certain patients with the disease (see **Releasing Brakes on the Immune System**, p. 83). In addition, the first liquid biopsy test was approved by the FDA for use in identifying which patients with metastatic NSCLC may benefit from treatment with the EGFR therapeutic erlotinib.

A biopsy is the removal of cells or tissues from a patient for testing to help physicians diagnose a condition such as cancer or monitor how it changes in response to treatment. Traditionally, biopsies are invasive procedures. However, research has shown that during the course of cancer development and treatment, tumors routinely shed detectable cells, lipid-encapsulated sacs called exosomes,

FIGURE 13

QUICK WORK AGAINST THE LEADING CAUSE OF CANCER DEATH



Lung cancer is the leading cause of cancer-related death in the United States (3). In the 12 months covered by the report, from Aug. 1, 2015, to July 31, 2016, the U.S. Food and Drug Administration (FDA) made eight decisions that have provided new hope for many patients diagnosed with lung cancer. In October 2015, the FDA approved two immunotherapeutics that work by releasing the PD-1 brake on immune cells called T cells for treating certain patients with non–small cell lung cancer (NSCLC). The first was pembrolizumab (Keytruda), which was approved for treating advanced NSCLC that has progressed after other treatments and tests positive for the protein PDL1 using the PD-L1 IHC 22C3 pharmDx test—a companion diagnostic that was approved alongside the immunotherapeutic. The second was nivolumab (Opdivo), which was approved for treating patients with advanced NSCLC that has progressed after treatment with a platinum-based traditional chemotherapeutic. In November 2015, the FDA approved the molecularly targeted therapeutic osimertinib (Tagrisso) for treating advanced NSCLC that tests positive for EGFR mutations using the cobas EGFR Mutation Test v2 and that has become resistant to other EGFR-targeted therapeutics. The FDA also approved necitumumab (Portrazza) for treating advanced squamous NSCLC. Alectinib (Alecensa) is a molecularly targeted therapeutic that was approved by the FDA for treating advanced NSCLC fueled by ALK mutations that has become resistant to the ALK-targeted therapeutic crizotinib (Xalkori) in December 2015. In March 2016, the approved uses of crizotinib were expanded to include the treatment of advanced NSCLC fueled by ROS1 mutations. Another treatment for advanced squamous NSCLC, the molecularly targeted therapeutic afatinib (Gilotrif), was approved in April 2016. The cobas EGFR Mutation Test v2 was approved by the FDA for testing plasma, the colorless liquid component of blood, for the presence of EGFR mutations in June 2016.

and free DNA into a patient's blood. Researchers have shown in clinical trials that it is possible to use a blood sample, or liquid biopsy, rather than a traditional tissue biopsy, to obtain material that can be analyzed to provide information about the genomic alterations in a patient's cancer. Liquid biopsies have the potential to transform patient care across the clinical cancer care continuum.

The revolution in cancer diagnosis and monitoring began in June 2016, when the FDA approved the first liquid biopsy companion diagnostic test for identifying whether or not a patient with metastatic NSCLC is eligible for treatment with the EGFR-targeted therapeutic erlotinib. The cobas EGFR Mutation Test v2 was already approved by the FDA for testing tumor tissue samples obtained by a traditional biopsy. The new approval allows the test to be used to analyze plasma, the colorless liquid component of blood.

Triggering Leukemia Cell Death

CLL is the second most common type of leukemia diagnosed in the United States, with almost 19,000 new cases projected to be diagnosed in 2016 (3). Tremendous progress has been made against CLL in the past 2 years, with several new molecularly targeted therapeutics approved by the FDA for treating patients with the disease, like **David Rampe** [who was featured in the *AACR Cancer Progress Report 2014* (1)].

DAVID RAMPE \\ AGE 58

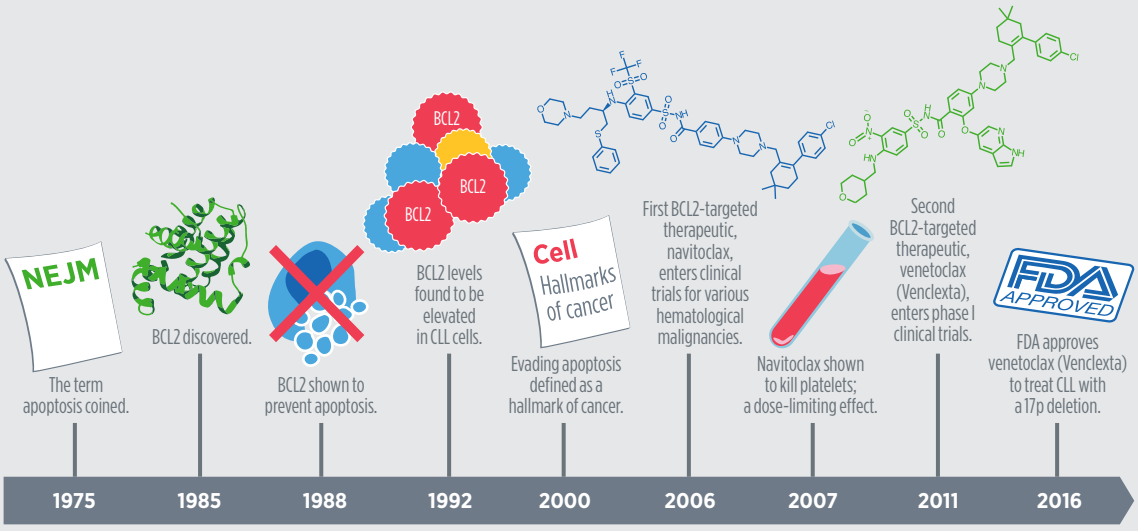
LIVING WITH CLL SINCE 2006

Although the new therapeutics benefit many patients with CLL, not all patients have a response to these treatments. Moreover, many patients whose CLL initially responds eventually have disease progression. Patients who have CLL characterized by a genetic mutation called the 17p deletion are particularly prone to poor outcomes.

In April 2016, the FDA approved the molecularly targeted therapeutic venetoclax (Venclexta) for treating CLL shown to have a 17p deletion with the Vysis CLL FISH Probe Kit companion diagnostic. This approval provided new hope to patients like **Brian Parkinson** (see p. 76).

FIGURE 14

CUTTING CANCER'S LIFELINE



Venetoclax (Venclexta) is a molecularly targeted therapeutic that works by blocking the protein BCL2, which promotes cell survival by preventing cells from undergoing a natural self-destruct process called apoptosis. It is currently the only anticancer therapeutic of its kind to be approved by the U.S. Food and Drug Administration (FDA). Many years of basic, translational, and clinical research underpinned the development of venetoclax. The term apoptosis was first coined in 1975. A decade later, researchers discovered BCL2 and then went on to show that its function was to prevent apoptosis. The development of the first BCL2-targeted therapeutic to enter clinical trials, navitoclax, was hampered by the fact that it causes platelet death, which limits the dose that can be given. Venetoclax was approved for treating patients with chronic lymphocytic leukemia (CLL) shown to have a 17p deletion with the Vysis CLL FISH Probe Kit companion diagnostic in April 2016.

“Venetoclax offered me the better chance to maintain my quality of life ...”

CLIMBING MOUNTAINS THANKS TO VENETOCLAX

BRIAN PARKINSON \\ AGE 60 \\ MILAN, ILLINOIS

IT IS ESTIMATED THAT 18,960 NEW CASES OF **CHRONIC LYMPHOCYTIC LEUKEMIA** WILL BE DIAGNOSED IN THE UNITED STATES IN 2016

© Dave Pierro

When my chronic lymphocytic leukemia (CLL) relapsed, I was training to climb Mount Denali, in Alaska. My doctor told me I had a choice of more chemotherapy or the last spot in a clinical trial testing venetoclax (Venclexta), which at the time was called ABT-199. After lots of research, I chose the clinical trial, although it meant postponing my climb. I felt that the clinical trial would give me the best chance for maintaining my quality of life, and it has. I'm off to climb Mount Elbrus, an 18,500-foot peak in Russia, in a few weeks.

I was first diagnosed with CLL in 2010, but my journey with leukemia began the previous fall, during what was a cold and wet harvest season on the farm. I had a cold that would just not go away. I hadn't seen a doctor in decades. So, after Thanksgiving, I went to a local urgent care center. They told me I had pneumonia and gave me antibiotics. Unfortunately, one course was not enough, and only after several courses did I finally feel better.

At that point, I decided I should have a routine physical. As part of the check-up, I had a blood test. The doctor called the next day to tell me the blood test had found a problem and that he had scheduled an appointment for me with an oncologist for that day. When I reached the oncologist's office, he told me, "You are really sick, and I have an appointment made for you at the hospital. You have to be there in half an hour because if we wait any longer than that, you may die."

It turned out the reason I needed to get to the hospital quickly was that my blood was so full of leukemia cells that they could have blocked my blood vessels at any moment, causing me to have a stroke.

In the hospital, I underwent leukopheresis to clean up my blood. Then, I had to decide whether to be treated locally or at a large center farther away. After researching the options, I chose to be treated at Northwestern Memorial Hospital in Chicago because it was a leading research hospital that gave me access to world-renowned doctors and clinical trials.

A battery of tests at Northwestern finally led to a diagnosis of CLL. After a 6-month course of chemotherapy, my doctor told me there were no signs of leukemia in my body, but he was very careful not to say that I was cured.

Sure enough, 4 years later, one of my routine blood tests revealed that the leukemia was back.

My doctor told me that in the 4 years since my initial diagnosis, research had led to a large number of treatments for people in my situation who were being tested in clinical trials. He also told me there was one spot left in a clinical trial he was involved with that was testing venetoclax or that I could be treated with chemotherapy, but a stronger chemotherapy than before.

The first chemotherapy treatment I had received had not given me many side effects, apart from losing my appetite. However, I did not want to start down the road of taking stronger and stronger chemotherapies and lose my quality of life. Venetoclax offered me a better chance to maintain my quality of life, so I opted for the clinical trial.

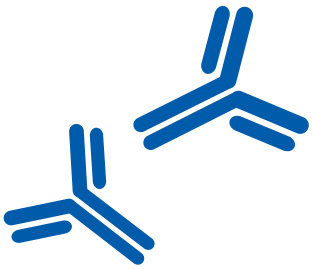
I continue to take venetoclax every day. I take four pills in the morning after breakfast. Once every 3 months, I go to Northwestern for follow-up appointments. They do some blood tests, and I usually have a CT scan. Then I see the doctor, who tells me I'm doing great and to keep up the good work. I can take advantage of the trip to the city and do something fun, like sail on Lake Michigan.

As far as I'm aware, I have no side effects from venetoclax. I am a little stiff in the morning, but I'm 60 years old, and once I'm up and about, I'm great. Really, really great.

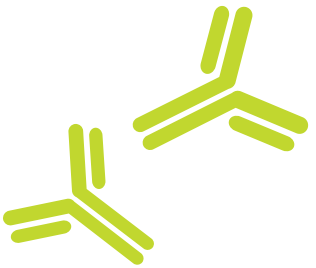
One thing I always tell people, and I've found myself counseling a lot of patients on the cancer floor at Northwestern over the years, is that having cancer is not an excuse to do nothing—you have to go out there and kick some butt.

RECENT ADVANCES AGAINST MULTIPLE MYELOMA

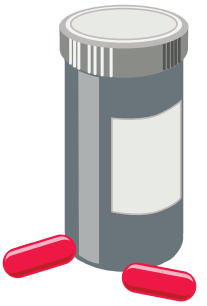
Daratumumab (Darzalex) is an immunotherapeutic that was approved by the FDA in November 2015 for treating multiple myeloma that has progressed despite treatment with at least three prior therapies, including a proteasome inhibitor and an immunomodulatory agent.



Elotuzumab (Empliciti) is an immunotherapeutic that was approved by the FDA in November 2015 for use in combination with lenalidomide (Revlimid) and dexamethasone for multiple myeloma that has progressed despite treatment with one to three prior treatments.



Ixazomib (Ninlaro) is a proteasome inhibitor that was approved by the FDA in November 2015 for use in combination with lenalidomide and dexamethasone for treating multiple myeloma that has progressed despite treatment with at least one prior treatment.



Venetoclax is the first in a new class of anticancer therapeutics called BCL2 inhibitors. BCL2 is a protein that promotes cell survival by preventing cells from undergoing a natural self-destruct process called apoptosis (see **Figure 14**, p. 75). CLL cells often express elevated levels of BCL2, and by blocking this protein, venetoclax triggers the cells to die by apoptosis.

The approval of venetoclax by the FDA was based on phase II clinical trial results showing that venetoclax benefited the majority of patients with CLL with a 17p deletion that had progressed despite treatment with at least one other therapeutic (142).

Each of the four new molecularly targeted therapeutics approved for treating CLL in the past 3 years—obinutuzumab, ibrutinib (Imbruvica), idelalisib (Zydelig), and venetoclax—targets a different molecule involved in CLL biology. This highlights how our increasing knowledge of a given cancer, which is gained through research, can yield multiple new approaches to treatment.

Making Treatment More Convenient

The number of treatment options for patients with multiple myeloma—one of the most commonly diagnosed hematological malignancies, or blood cancers, in the United States—has dramatically increased in the past decade.

Two of the molecularly targeted therapeutics approved by the FDA for treating multiple myeloma in this period target the proteasome. The proteasome is a machine naturally found in cells that breaks down proteins the cell no longer needs. This process helps control cell division and survival. By preventing the natural breakdown of proteins, these two therapeutics, bortezomib (Velcade) and carfilzomib (Kyprolis), are highly toxic to myeloma cells, causing them to die.

Bortezomib and carfilzomib are administered to patients by injection, either into the veins or, in the case of bortezomib, under the skin. In November 2015, the FDA approved the first proteasome inhibitor that can be taken by mouth, ixazomib (Ninlaro), providing patients with multiple myeloma with a more convenient treatment option.

Ixazomib is intended for use in combination with the immunomodulatory agent lenalidomide (Revlimid) and the steroid dexamethasone to treat patients with multiple myeloma that has progressed despite treatment with at least one prior therapy. Its approval was based on the fact that adding ixazomib to lenolidamide and dexamethasone significantly increased the average time before disease progressed for patients enrolled in a phase III clinical trial (143).

Ixazomib is just one of three new therapeutics approved in November 2015 for treating multiple myeloma (see sidebar on **Recent Advances Against Multiple Myeloma**). The other two therapeutics work by exploiting the power of the immune system and are discussed in **Directing the Immune System to Cancer Cells** (see p. 90).

Combining Therapeutics to Improve Outcomes

Melanoma is the deadliest form of skin cancer: It accounts for only 1 percent of all U.S. skin cancer cases but the majority of skin cancer deaths (3). Before Jan. 1, 2011, the FDA had not approved a new systemic treatment for melanoma in more than 20 years. Since that time, the agency has approved a wide array of molecularly targeted therapeutics and immunotherapeutics, for use as single agents or in combination, to treat patients with metastatic melanoma (see **Figure 15**).

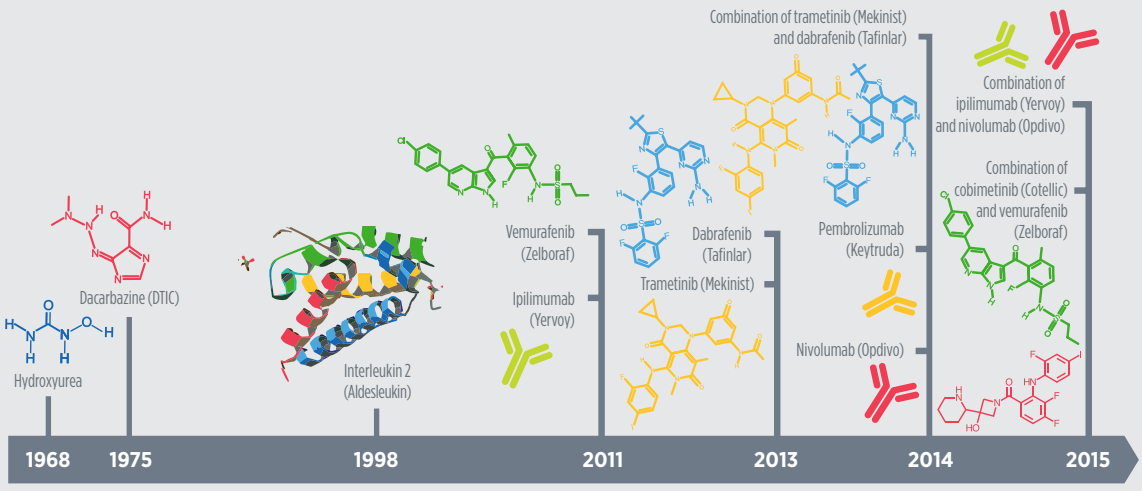
The most recent of these approvals came in November 2015, when the FDA approved a combination of molecularly targeted therapeutics, cobimetinib (Cotellic) and vemurafenib (Zelboraf), for treating metastatic melanoma fueled by certain mutations in the BRAF gene.

About 50 percent of melanomas are driven by genetic mutations that lead to an abnormal protein called BRAF V600E (144). This knowledge led to the development and subsequent FDA approval of two BRAF V600E–targeted therapeutics, vemurafenib and dabrafenib (Tafinlar). Although these molecularly targeted therapeutics benefit many patients with melanoma fueled by the BRAF V600E protein, the majority of those whose cancers initially respond to vemurafenib and dabrafenib have disease progression within a year of starting treatment owing to treatment resistance (145, 146).

Trametinib and cobimetinib block the activity of two proteins, MEK1 and MEK2, that function in the same signaling network as abnormal BRAF proteins. Trametinib is FDA approved for use alone or in combination with dabrafenib for treating patients with metastatic

FIGURE 15

MAKING UP FOR LOST TIME



The DNA synthesis inhibitor hydroxyurea was the first therapeutic for the systemic treatment of metastatic melanoma approved by the U.S. Food and Drug Administration (FDA). Its approval in 1968 was followed by the approval of the DNA-damaging agent dacarbazine (DTIC) in 1975. Twenty-three years passed before another systemic therapeutic, the immune system stimulator recombinant interleukin-2 (aldesleukin; Proleukin), was approved for the treatment of melanoma. In 2011, ipilimumab (Yervoy) became the first immune-checkpoint inhibitor approved by the FDA and the first new systemic treatment for melanoma in 23 years. That year also saw the approval of vemurafenib (Zelboraf), a therapeutic that selectively inactivates the mutant form of the protein BRAF that occurs in approximately 50 percent of melanomas. In 2013, the FDA approved a second mutant BRAF–targeted agent, dabrafenib (Tafinlar), as well as trametinib (Mekinist), a therapeutic that targets other proteins in the BRAF signaling pathway, MEK1 and MEK2. The combination of dabrafenib and trametinib was FDA approved in 2014, as were two new immune-checkpoint inhibitors, nivolumab (Opdivo) and pembrolizumab (Keytruda). In 2015, the FDA approved the use of ipilimumab and nivolumab in combination, as well as a new MEK-targeted therapeutic, cobimetinib (Cotellic), for use in combination with vemurafenib for the treatment of BRAF-mutant metastatic melanoma. Note: this timeline focuses on systemic, primary treatments for regional and metastatic melanoma; other therapeutics have been approved for the prevention of disease recurrence or the treatment of localized lesions (see **Supplemental Table 2**, p. 131).

Figure adapted from Ref. (24)

62,700

new cases of kidney and renal pelvis cancer are expected to be diagnosed in the United States in 2016 (3). Renal cell carcinoma is the most common form of kidney cancer diagnosed in U.S. adults.

melanoma shown to be fueled by either BRAF V600E or another abnormal BRAF protein called BRAF V600K. The combination of dabrafenib and trametinib almost doubles the length of time before metastatic melanoma becomes resistant to treatment and progresses compared with either molecularly targeted therapeutic used alone (147).

Similarly, adding cobimetinib to vemurafenib significantly increased the time before disease progressed for patients with metastatic melanoma fueled by BRAF V600E or BRAF V600K, as determined in a phase III clinical trial using the FDA-approved companion diagnostic cobas 4800 BRAF V600 Mutation Test (144).

The combinations of dabrafenib and trametinib, and cobimetinib and vemurafenib, are the first molecularly targeted therapeutic combinations to have been approved by the FDA for treating any type of cancer. As our understanding of the biology of cancer continues to grow, it is highly likely that combinations of molecularly targeted therapeutics will become an integral part of cancer treatment in the near future.

Blocking the Blood Supply to Tumors

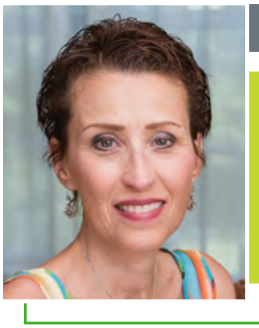
Research has shown that many solid tumors need to establish their own blood and lymphatic vessel network to grow and survive. It has also led to the identification of many molecules that control the growth of the new blood and lymphatic vessels within a tumor, as well as the development of anticancer therapeutics that specifically target these molecules. These molecularly targeted therapeutics are sometimes referred to as antiangiogenic therapeutics. Currently, there are 11 such therapeutics to have been approved by the FDA.

In many cases, antiangiogenic therapeutics not only target molecules that stimulate blood and lymphatic vessel growth, but they also target molecules that promote tumor growth and cancer progression in other ways, such as triggering cancer cell multiplication.

Many antiangiogenic therapeutics are approved by the FDA for treating a number of different types of cancer.

In April 2016, the FDA increased the number of types of cancer for which the antiangiogenic agent cabozantinib can be used as a treatment, when it approved a tablet form of the molecularly targeted therapeutic (Cabometyx) for treating patients with advanced renal cell carcinoma that has progressed despite treatment with at least one other antiangiogenic therapeutic. This approval was based on results from a phase III clinical trial comparing cabozantinib with everolimus (Afinitor)—a recommended treatment for patients with renal cell carcinoma who have previously received one or more antiangiogenic therapeutics (see **Expanding the Use of an Anticancer Therapeutic**) (148). The trial showed that cabozantinib increased the time before disease progressed and improved survival. The April 2016 approval followed the November 2012 FDA approval of a capsule form of cabozantinib (Cometriq) for treating patients with metastatic thyroid cancer.

In May 2016, the FDA approved a second use for the antiangiogenic therapeutic lenvatinib (Lenvima), when it approved it for use in combination with everolimus for treating patients with advanced renal cell carcinoma that has progressed despite treatment with at least one other antiangiogenic therapeutic. The approval was based on the fact that adding lenvatinib to everolimus increased the time before disease progressed and improved survival for patients enrolled in a phase II clinical trial (149). The first use for lenvatinib was approved by the FDA in February 2015: It was approved for treating patients with metastatic differentiated thyroid cancer like **Lori Cuffari** [who was featured in the *AACR Cancer Progress Report 2015* (24)].



LORI CUFFARI \\ AGE 52

SURVIVING HURTHLE CELL CANCER THANKS TO CLINICAL TRIALS (24).

These new approvals both expand the number of patients who may benefit from the antiangiogenic therapeutics and increase the return on prior investments in biomedical research.

Expanding the Use of an Anticancer Therapeutic

Everolimus is another molecularly targeted therapeutic to have its use in clinical cancer care expanded by the FDA in the 12 months leading up to July 31, 2016. In February 2016, it was approved for treating certain patients with neuroendocrine tumors—those with progressive, well-differentiated, nonfunctional, neuroendocrine tumors

of gastrointestinal or lung origin that cannot be removed by surgery or that have progressed. The latest approval came almost 7 years after the first, which was for treating patients with renal cell carcinoma that has progressed despite treatment with an antiangiogenic therapeutic (see **Blocking the Blood Supply to Tumors**, p. 80).

Everolimus targets a protein called mTOR, which research has shown is part of a signaling network that promotes several important cellular processes, including cell multiplication. Research has also shown that the mTOR signaling network is excessively active in many types of cancer. Thus, one rationale for testing everolimus as an anticancer therapeutic is that it can dampen the excessive mTOR signaling network activity that helps fuel cancer cell multiplication.

In fact, blocking mTOR with everolimus almost tripled the time before disease progressed, compared with placebo, for patients with advanced, progressive, well-differentiated, nonfunctional, neuroendocrine tumors of gastrointestinal or lung origin enrolled in a phase III clinical trial (150).

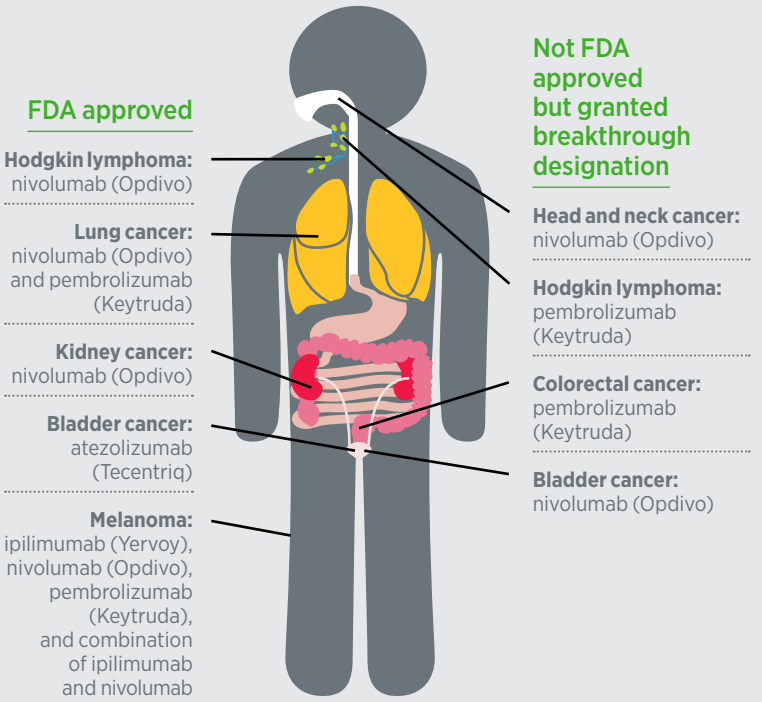
Neuroendocrine tumors are a group of cancers that form from neuroendocrine cells, which are cells that release hormones into the blood in response to a signal from the nervous system. Although they can arise anywhere in the body that there are neuroendocrine cells, more than 80 percent arise in the gastrointestinal tract, lungs, or pancreas (151). The new approval for everolimus, combined with its May 2011 approval for treating patients with advanced, progressive neuroendocrine tumors of pancreatic origin, made it the first molecularly targeted therapeutic to have shown anticancer activity across much of the spectrum of neuroendocrine tumor types.

Treatment With Immunotherapeutics

In the past 5 years, immunotherapy has emerged as one of the most exciting new approaches to cancer treatment that has ever entered the clinic. This is in part because some of the patients who have been treated with these revolutionary anticancer treatments have had remarkable and durable responses, raising the possibility that they might be cured, and also in part, because some of the immunotherapeutics have been shown to benefit patients with an increasing number of types of cancer (see **Figure 16**). In fact, one immunotherapeutic, nivolumab (Opdivo), was recently approved by the FDA for four new uses in just 12 months (see **Releasing Brakes on the Immune System**, p. 83).

FIGURE 16 THE EXPANDING SCOPE OF CANCER IMMUNOTHERAPEUTICS

AS OF JULY 31, 2016, THE FOLLOWING CHECKPOINT INHIBITORS WERE:



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 the brakes on the natural cancer-fighting power of immune cells called T cells. These revolutionary anticancer agents are called checkpoint inhibitors. They have yielded remarkable and durable responses for some patients with an increasingly broad array of cancer types. As of July 31, 2016, the FDA has approved four checkpoint inhibitors: atezolizumab (Tecentriq), ipilimumab (Yervoy), nivolumab (Opdivo), and pembrolizumab (Keytruda). The cancers for which these immunotherapeutics have been approved or have been granted FDA breakthrough designation are highlighted in the figure.

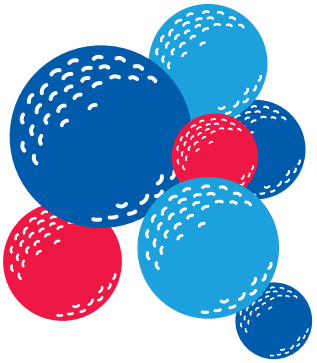
HOW IMMUNOTHERAPEUTICS WORK

The way in which different immunotherapeutics work to benefit patients varies:

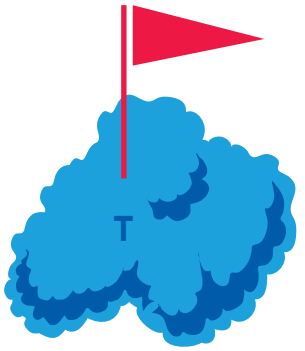
Some release the brakes on the natural cancer-fighting power of the immune system, for example, atezolizumab (Tecentriq) (see **Releasing Brakes on the Immune System**, p. 83).

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).

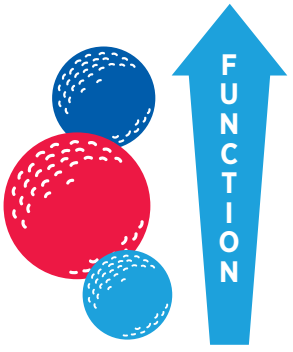
Some increase the killing power of the immune system by providing more cancer-targeted immune cells called T cells; these are called adoptive T-cell therapies, for example CTL019 and JCAR015 [for more information on these immunotherapeutics see the *AACR Cancer Progress Report 2015* (24)].



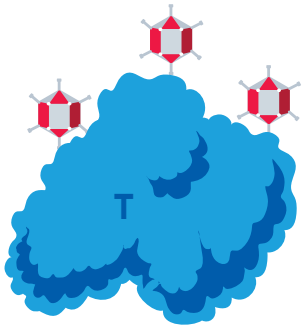
Some flag cancer cells for destruction by the immune system, for example, daratumumab (Darzalex) and elotuzumab (Empliciti) (see **Directing the Immune System to Cancer Cells**, p. 90).



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) (see **Boosting the Killing Power of the Immune System**, p. 90).



Adapted from (1)

Cancer immunotherapy refers to therapeutics that can unleash the power of a patient's immune system to fight cancer the way it fights pathogens. These therapeutics are called immunotherapeutics. Not all immunotherapeutics work in the same way (see sidebar on **How Immunotherapeutics Work**, p. 82).

Given that our scientific understanding of the immune system and how it interacts with cancer cells is rapidly increasing, there are many novel immunotherapeutics in development and new ways being tested to use those that we already have. The new agents and treatment strategies that are on the horizon hold extraordinary promise for the future. A glimpse of this future is discussed in **Anticipating Future Progress** (see p. 100). Here, we focus on immunotherapeutics that were approved by the FDA in the 12 months covered by this report, Aug. 1, 2015 to July 31, 2016.

Releasing Brakes on the Immune System

Research has shown that immune cells called T cells are naturally capable of destroying cancer cells (see sidebar on **Key Players in the Immune System**, p. 86). 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. Brakes on the surface of T cells are called immune-checkpoint proteins.

This knowledge has led researchers to look for ways to release the brakes on T cells.

As of July 31, 2016, the FDA has approved four immunotherapeutics that work by releasing brakes on the immune system for treating certain patients with a growing array of cancer types (see **Figure 16**, p. 81). In March 2011, ipilimumab (Yervoy) was the first of these agents to be approved, after it was shown to be the first treatment ever to extend overall survival for patients with metastatic melanoma (see **Figure 15**, p. 79) (152). Ipilimumab targets the immune-checkpoint protein CTLA-4, protecting it from the proteins that attach to it and trigger it to put the brakes on T cells.

Nivolumab and pembrolizumab (Keytruda) are the second and third immunotherapeutics that work by releasing brakes on the immune system. They target an immune-checkpoint protein called PD-1, which applies brakes to T cells after attaching to PD-L1 or PD-L2. Nivolumab and pembrolizumab work by preventing PD-1 from attaching to PD-L1 and PD-L2, thereby releasing the brakes on T cells. They were both approved by the FDA for treating patients with metastatic melanoma in late 2014. Longer follow-up of patients enrolled in some of these clinical trials recently revealed that more than one third of patients who received nivolumab are still alive 5 years after starting treatment and that 49 percent of patients who received pembrolizumab are still alive 2 years after starting treatment (153). These numbers are extremely exciting given that the 5-year relative survival rate for patients with metastatic melanoma diagnosed between 2005 and 2011 was just 17 percent (3).

In 2015, nivolumab and pembrolizumab were both approved by the FDA for treating certain patients with advanced lung cancer whose disease has progressed during or after other treatments. In the case of nivolumab, it was approved in March of that year for treating patients with the squamous cell type of NSCLC and in October 2015, for patients with the more common nonsquamous cell type of NSCLC, like **Donna Fernandez** [who was featured in the *AACR Cancer Progress Report 2015* (24)]. These approvals were based on the fact that in phase III clinical trials, nivolumab extended overall survival for patients compared with the cytotoxic chemotherapeutic docetaxel, which is standard of care for patients with advanced NSCLC that has progressed during or after initial chemotherapy (154, 155).

DONNA FERNANDEZ \\ AGE 62

SURVIVING LUNG CANCER THANKS TO IMMUNOTHERAPY (24).

In October 2015, pembrolizumab was approved for treating patients with advanced NSCLC that has progressed during or after other treatments. At the same time, the FDA also approved the PD-L1 IHC 22C3 pharmDx test, a companion diagnostic for identifying those patients for whom pembrolizumab is a treatment option—those whose tumors have the PD-L1 protein on their surface. These decisions were based on clinical trial results showing that pembrolizumab treatment led to tumor shrinkage in more than 40 percent of patients with advanced NSCLC positive for PD-L1 using the PD-L1 IHC 22C3 pharmDx test (156). Subsequent results from another clinical trial showed that the immunotherapeutic improved overall survival compared with docetaxel (157).

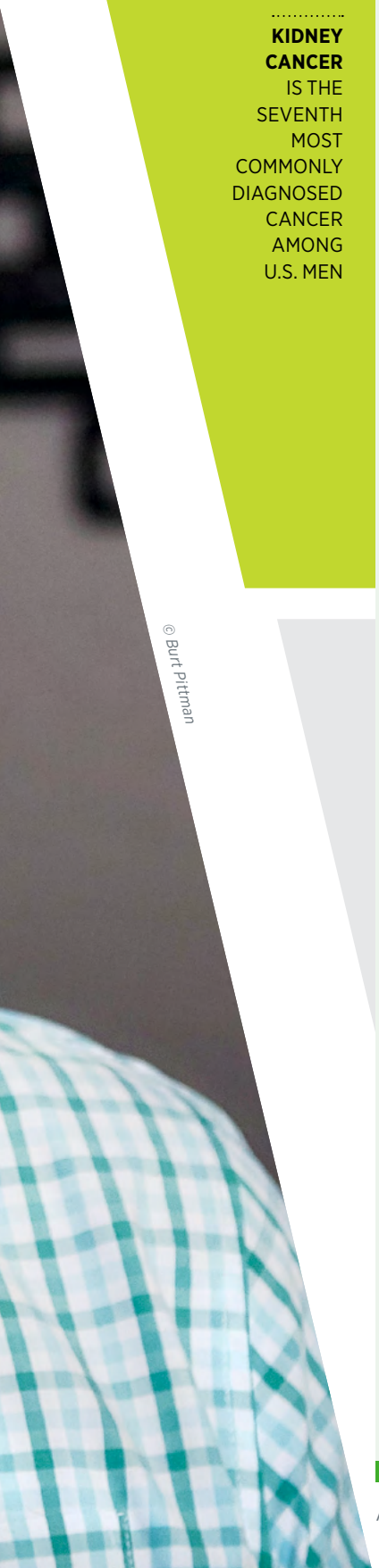
The number of cancer types for which nivolumab is an FDA-approved treatment option was recently expanded to include renal cell carcinoma and Hodgkin lymphoma, providing new hope for patients like **Philip Prichard** (see p. 84). In November 2015, it was approved for treating patients

“I’m living proof that immunotherapy works ...”

LOOKING FORWARD TO THE FUTURE THANKS TO NIVOLUMAB

PHILIP PRICHARD \\ AGE 51 \\ MEMPHIS, TENNESSEE

KIDNEY CANCER IS THE SEVENTH MOST COMMONLY DIAGNOSED CANCER AMONG U.S. MEN



© Burt Pittman

In February 2013, I was told that I had about 18 months to live because my kidney cancer had spread throughout my body. After seeking out a second opinion at The University of Texas MD Anderson Cancer Center in Houston, I started receiving nivolumab (Opdivo) through a clinical trial. There is now no evidence of cancer in my body, and I'm looking forward to enjoying life, building a new company, and traveling the world with my wife.

My journey with kidney cancer began in July 2012 when my wife insisted that I go to the doctor. I had been really tired and lethargic for a while, sleeping the weekends away, and my blood pressure had risen dramatically. But the deciding factor for my wife was when I saw blood in my urine.

During the exam, the doctor felt around my abdomen and said, "That's not supposed to be there." He went on to explain to my wife and me that I had a large mass on my kidney and I needed a CT scan immediately. I was in shock, even more so when the scan confirmed I had kidney cancer. This all happened on a Monday. That Friday, I had surgery here in Memphis, and the surgeon removed my right kidney and a 3.8-pound tumor.

Tests showed that the tumor was a type of kidney cancer called renal cell carcinoma. This finding led my oncologist to start me on pazopanib (Votrient). Despite this, after I had recovered from surgery, I felt pretty good and went back to work.

Then, in November 2012, a routine follow-up scan showed that the cancer had spread, and there was a tumor wrapped around my adrenal gland. We scheduled a second surgery but had to put it off after I developed a blood clot in my lung. I spent 5 days in the hospital over the New Year being treated with blood thinners.

Once the blood clot had been treated, I was able to schedule the surgery again. By this time, it was February 2013. When I woke up from the operation, all the surgeon would say was, "We will talk later." I knew things were not good. It turned out that he hadn't been able to remove the tumor because it had spread throughout my abdomen. It was not just on my adrenal gland but also wrapped around my vena cava [the large blood vessel that carries blood back to the heart] and in my liver.

At this point, my health was deteriorating rapidly. I was losing weight and feeling extremely lethargic. I was down to just 190 pounds and could barely get around by myself.

It looked as if chemotherapy was my only option, but it offered me no hope. So my wife and I decided we would get a second opinion and went to the University of Texas MD Anderson Cancer Center in Houston. The doctor there, Dr. Tannir, confirmed that surgery was not an option for me but told us about a clinical trial testing a new drug that would turn on my immune system to fight the cancer. This new information gave us some hope, and I had no hesitation in enrolling in the nivolumab clinical trial.

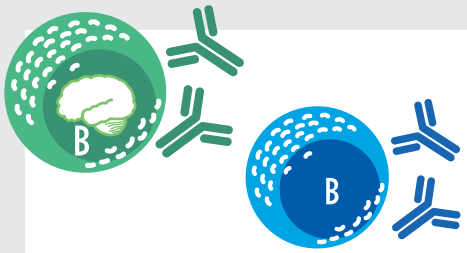
I started receiving nivolumab in March 2013 and was treated every 2 weeks. Within a month or so, I began feeling better. I was less tired, I could feel myself getting stronger, and I started gaining weight. After the first 3 months, scans showed that the tumors had reduced by 30 percent. This news lifted my spirit. My spirit has lifted even more with every scan since, because each one showed that the tumors were shrinking more and more.

Currently, there is no evidence of disease, just a little scar tissue in my liver, which I will have surgically removed in the near future. I am so healthy that 3 years after I started taking nivolumab, Dr. Tannir decided that I do not need to take it anymore.

I'm living proof that immunotherapy works, and I can't stress enough how much the research funding that led to drugs like nivolumab means to me. Nivolumab gave me hope again. I can live life and see the future.

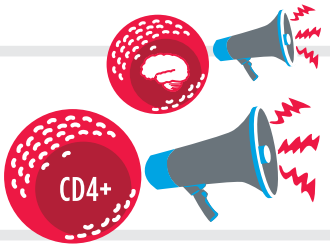
KEY PLAYERS IN THE IMMUNE SYSTEM

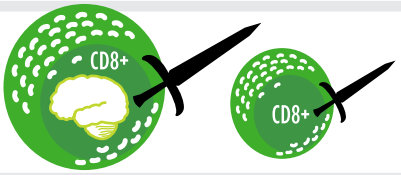
White blood cells are the cells of the immune system that work together to protect the body from pathogens. They can also cooperate to attack and destroy cancer cells. Here, we describe briefly the unique functions of the white blood cells that have a central role in these processes.



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

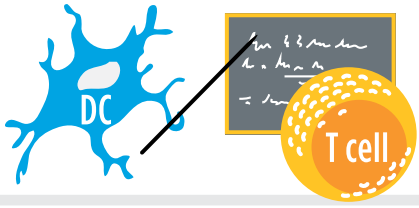
CD4+ T cells help manage the immune response. Some remain as memory T cells to fight again later.





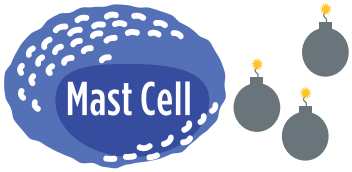
CD8+ T cells kill infected, damaged, and cancer cells. Some remain as memory T cells to fight again later.

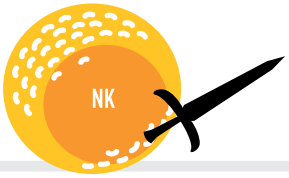
Dendritic cells educate T cells about what kinds of cells they should and should not attack.



Macrophages eat foreign materials.

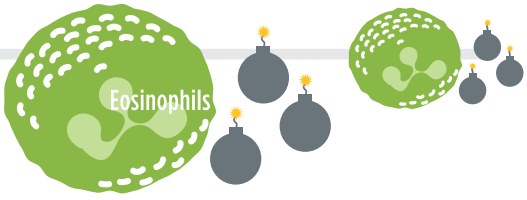
Mast cells release chemicals against pathogens and stimulate the immune system.





Natural killer (NK) cells kill infected, damaged, and cancer cells.

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



with advanced renal cell carcinoma that has progressed despite treatment with at least one antiangiogenic therapeutic after it was shown to improve overall survival for patients enrolled in a phase III clinical trial compared with everolimus, a recommended treatment in this situation (158) (see **Blocking the Blood Supply to Tumors**, p. 80). The approval for Hodgkin lymphoma came in May 2016, after results from early-stage clinical trials showed that it caused partial or complete shrinkage of tumors in the majority of patients with classical Hodgkin lymphoma that had relapsed or progressed despite treatment with an autologous hematopoietic stem cell transplant and post-transplantation brentuximab vedotin (Adcetris) (159).

Hodgkin lymphoma
is a rare type of cancer;
it is expected that there will be
8,500 new cases
of the disease diagnosed
in the United States in 2016.

The fourth immunotherapeutic to be approved by the FDA that works by releasing brakes on the immune system is atezolizumab (Tecentriq). Atezolizumab targets PD-L1, preventing it from attaching to PD-1 and triggering its brake function. It also prevents PD-L1 from attaching to and triggering another brake on T cells called B7.1 (160). In May 2016, atezolizumab was approved for treating patients with locally advanced or metastatic urothelial carcinoma that has progressed despite treatment with a platinum-based cytotoxic chemotherapeutic. The decision was based on the fact that atezolizumab treatment led to partial shrinkage or complete disappearance of tumors for patients enrolled in a phase II clinical trial (161). This approval provides tremendous hope for patients with urothelial carcinoma because atezolizumab is the first new treatment shown to improve outcomes for patients, like **Dave Maddison** (see p. 88), in 30 years.

The spectacular successes highlighted here have motivated researchers to begin testing these revolutionary immunotherapeutics as a potential treatment for numerous other types of cancer. Results are not yet available for most of these clinical trials. However, initial results show that nivolumab and pembrolizumab may benefit some patients with head and neck cancer (162, 163), and that pembrolizumab may benefit a subgroup of patients with colorectal cancer (164).

Despite the tremendous achievements, treatment with FDA-approved immunotherapeutics that work by releasing brakes on the immune system does not yield remarkable and long-term responses for all patients. As a result, researchers are testing various ways to help increase the number of patients who may benefit from these immunotherapeutics, including evaluating how well they work in combination. The FDA approved the first of these combinations, ipilimumab and nivolumab, in September 2015, after it was shown in a phase II clinical trial that adding nivolumab to ipilimumab increased the percentage of patients with metastatic melanoma to have tumor shrinkage or disappearance more than five-fold (165).

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

Urothelial carcinoma
is the most common type of bladder cancer, which is the

fifth most commonly diagnosed cancer

in the United States (3)

and the

ninth most commonly diagnosed cancer

worldwide (8).

"... I have no doubt that research saved my life."

SURVIVING BLADDER CANCER THANKS TO RESEARCH

DAVE MADDISON \\ AGE 70 \\ BISHOPSTEIGNTON, UNITED KINGDOM

BLADDER CANCER IS THE SIXTH MOST COMMONLY DIAGNOSED CANCER AMONG MEN WORLDWIDE

© Rowan Johnson

I was diagnosed with bladder cancer in February 2009. After 5 years in which I had three major surgeries and what seemed like endless months of radiotherapy and chemotherapy, which made me really, really sick, I was told to put my affairs in order. But then, I was offered a spot in a clinical trial testing an immunotherapy called atezolizumab (Tecentriq), and I'm now the picture of health. I start work at 7:15 each morning and spend my spare time in the garden, doing jobs around the house, and building memories with my family.

My journey with bladder cancer started very suddenly, toward the end of 2008, when I noticed my urine was bright red. It was a huge shock, and I immediately made an appointment with my physician. About 8 weeks later, after lots of poking, prodding, tests, and scans, I was told that I had a tumor on the tube [ureter] that connected my right kidney to my bladder.

I was filled with fear. Fear of suffering, fear of pain, and fear of dying.

After a 9 ½ hour surgery to remove the tumor and my right kidney, the doctors told me there was no sign that the cancer had spread and that I didn't need to have chemotherapy.

But 6 to 8 months after the surgery, a follow-up scan showed that a tumor had developed where the kidney had been removed. So my oncologist started me on a 4-month course of chemotherapy—gemcitabine and cisplatin. The day after my first infusion, I collapsed at home and had to be taken to the hospital, as I was so sick. That was just the first day of 4 months of hell. I couldn't keep food down, one particular brand of grapefruit juice made up about 60 percent of my diet, I had extreme constipation, and my quality of life was about 15 percent of normal.

Over the next few years, I had radiotherapy and more chemotherapy in an effort to keep my cancer at bay. But by February 2014, I had 11 tumors in my body, nine in my right lung, one in my lymph system above my stomach, and the primary tumor in my pelvis, which was the size of a grapefruit. My oncologist told me there was nothing more she could do and that I had 8 months to a year left to live.

To make sure she left no stone unturned, she referred me to another oncologist who she said would know about all the oncology clinical trials being conducted. I saw him 2 months later, and he connected me with Professor Thomas Powels at Barts Cancer Institute in London who he said had a clinical trial that would be a perfect fit for me.

After speaking with Professor Powels, I jumped at the 50/50 chance of living he said that the trial offered me. I've been receiving atezolizumab through the trial for the past 2 ½ years. I go to London every 3 weeks for a 1-hour infusion of the immunotherapy, and I've never had a single side effect, except a little fatigue in the afternoon.

After just nine infusions of atezolizumab, the doctors could no longer see 10 of my 11 tumors, and the primary tumor in my pelvis had shrunk to the size of a thumbnail. I was later offered the chance to stop taking atezolizumab, but I chose to continue with it. Why would I want to stop when it has turned my life around? Before I started taking atezolizumab, I was preparing for death. Now I can't get enough of life, and I'm so thankful to have been given the chance to share moments with my grandson that by all predictions should not have been possible.

For me, enrolling in the atezolizumab clinical trial was my last chance for life, and I got it. Today, I try to give back by telling my story. I speak to a lot of people at Barts who are considering a clinical trial. I tell them about my experience and answer their questions.

I also share my experience because I know I am the lucky beneficiary of research. Atezolizumab only came about because of immunotherapy research and the hard work and money that supported it, and I have no doubt research saved my life.

The U.S. multiple myeloma incidence rate has risen about 0.7% each year for the past 2 decades (2).

Directing the Immune System to Cancer Cells

Before an immune cell can destroy a cancer cell, it must find it. Many therapeutic antibodies that have been approved by the FDA for treating patients with a wide range of cancer types (see **Supplemental Table 2**, p. 131) work, at least in part, by helping immune cells find cancer cells. The most recent additions to this group of immunotherapeutics are daratumumab (Darzalex) and elotuzumab (Empliciti), which were both approved by the FDA in November 2015 for treating patients with multiple myeloma that has progressed despite treatment with a number of other therapeutics.

Multiple myeloma is one of the most commonly diagnosed hematological malignancies, or blood cancers, in the United States, with 30,330 new cases expected to be diagnosed in 2016 (3). In recent years, the development and FDA approval of new therapeutics—including proteasome inhibitors like bortezomib and carfilzomib and immunomodulatory agents like lenalidomide—have improved outcomes for patients like **Congressman Bob Carr**, who was featured in the *AACR Cancer Progress Report 2012* (87). Despite the advances, many patients whose disease initially responds to the new therapeutics eventually relapse owing to treatment resistance.

CONGRESSMAN M. ROBERT CARR \\ AGE 73

SURVIVING MULTIPLE MYELOMA THANKS TO CANCER RESEARCH (87).

Daratumumab works by attaching to a protein called CD38, which is found at high levels on the surface of myeloma cells. This attachment has several effects on the myeloma cells, most notably flagging them for immune cells, which upon attaching to another part of daratumumab are triggered to destroy the myeloma cells. Daratumumab was approved by the FDA after it was shown in early-stage clinical trials to lead to tumor shrinkage or disappearance in a significant number of patients whose multiple myeloma had relapsed despite several other treatments (167). It is hoped that future studies will reveal that the immunotherapeutic also extends survival for patients.

Elotuzumab attaches to another protein that is found at high levels on the surface of myeloma cells, SLAM7F. This protein is also found at high levels on immune cells called natural killer cells (see sidebar on **Key Players in the Immune System**, p. 86). Elotuzumab has distinct effects on myeloma cells and natural killer cells after attaching to SLAM7F on their surfaces, thus providing a two-pronged attack on multiple myeloma. It directly activates natural killer cells, enhancing their ability to kill myeloma cells, and it flags myeloma cells for a number of immune cell types, which once directed to the myeloma cells, attack and destroy them.

Elotuzumab was approved for use in combination with lenalidomide and dexamethasone for treating patients who have multiple myeloma that has worsened despite treatment with other therapeutics. This decision was based on phase III clinical trial results, which showed that adding elotuzumab to lenalidomide and dexamethasone significantly increased the number of patients who had their tumors shrink or disappear, as well as the time before disease progressed (168).

These approvals, together with the November 2015 approval of ixazomib (see sidebar on **Recent Advances Against Multiple Myeloma**, p. 78), have provided patients with multiple myeloma, like **Stephen Herz** (see p. 92), not only new treatment options, but also new hope.

Boosting the Killing Power of the Immune System

Another approach to cancer immunotherapy is to enhance the ability of T cells to eliminate cancer cells. If we use the analogy of a car, this approach is like stepping on the accelerator, and it can be done in a number of ways (see sidebar on **How Immunotherapeutics Work**, p. 82).

One form of immunotherapy that appears to work, in part, by boosting the killing power of the immune system is oncolytic virotherapy. Oncolytic viruses are viruses, which may or may not be genetically modified in some way, that can infect and destroy cancer cells. As the cancer cells are destroyed, they release molecules that can trigger immune cells that have the natural potential to destroy yet more cancer cells. These immunotherapeutics are injected directly into patients' tumors, rather than being given orally or by intravenous infusion.

More than
4%
of the U.S. population
are cancer survivors.

In October 2015, the first oncolytic virotherapeutic, talimogene laherparepvec (Imlygic), was approved by the FDA for the treatment of melanoma lesions in the skin and lymph nodes that cannot be removed completely by surgery.

The new immunotherapeutic, which was called T-Vec during development, is a herpes simplex virus (HSV) type 1 that has been genetically modified in a number of ways so that it is less able to cause disease, is more selective for cancer cells, and is more likely to promote an anticancer immune response. One of these modifications is the addition of a gene that provides the instructions for making an immune system–boosting factor called GM-CSF.

The exact way in which T-Vec works has not been definitively determined by researchers and remains an area of active investigation. However, it appears that after injection directly into melanoma lesions, T-Vec enters cancer cells, where it multiplies and promotes the production of GM-CSF. As it multiplies, T-Vec causes the cancer cells to rupture and die. Rupturing cancer cells release GM-CSF and cell contents that together can boost the killing power of the immune system.

T-Vec was approved after it was shown in a phase III clinical trial to significantly increase the number of patients who had skin and lymph node melanoma lesions shrink or disappear compared with GM-CSF (169). Even though T-Vec has not been shown to improve overall survival or to have an effect on melanoma that has spread to other parts of the body, it provides patients like **Bob Ribbans** (see p. 94) with new treatment options and new hope.

Living With or Beyond Cancer

Research is powering 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 Jan. 1, 2016, compared with just 3 million in 1971, and this number is projected to rise to 20.3 million by Jan. 1, 2026 (4, 169).

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 now commonly 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. Recent progress in cancer treatment was discussed in the previous three sections of the report (see **Treatment With Surgery, Radiotherapy, and Cytotoxic Chemotherapy**, p. 61, **Treatment With Molecularly Targeted Therapeutics**, p. 67, and **Treatment With Immunotherapeutics**, p. 81). 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 and highlights some of the challenges they continue to face (see sidebar on **Life After a Cancer Diagnosis in the United States**, p. 96).

Each phase of cancer survivorship is accompanied by a unique set of challenges. Moreover, 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), like **Jameisha (Meisha) Brown**, [who was featured in the *AACR Cancer Progress Report 2014* (1)], are particularly at risk for critical health-related problems because their bodies were still developing at the time of treatment (see sidebar on **Surviving a Cancer Diagnosis as a Child or Adolescent**, p. 97). 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.

JAMEISHA (MEISHA) BROWN \\ AGE 26

18-YEAR CHILDHOOD CANCER SURVIVOR AND CANCER HEALTH DISPARITIES RESEARCHER (1).

Importantly, 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.

BEATING MULTIPLE MYELOMA THANKS TO IMMUNOTHERAPY

STEPHEN (STEVE) HERZ // AGE 61 // WEST BABYLON, NEW YORK

Since my multiple myeloma relapsed in 2010, I have participated in a clinical trial testing an immunotherapeutic called elotuzumab (Empliciti) together with lenalidomide (Revlimid) and dexamethasone. The experience is so different from the one I had when I was initially treated 17 ½ years ago. Back then, I could barely leave the house for 3 years. Now, I have days when I can easily walk the 5-mile round trip to Fire Island Lighthouse on Long Island.

My long journey with cancer began in February 1998. I was trying to teach my daughter to figure skate. It was our first time out on the ice together, and I fell, breaking my hip into 17 pieces.

Shattering your hip into 17 pieces is not something that is supposed to happen to a 43-year-old man. So, while I was in the hospital having my hip screwed back together, the doctors ran a number of tests and discovered that I had stage 3 multiple myeloma. I had lytic bone lesions in several of my neck and back vertebrae and in my skull. I put my diagnosis down to being exposed to radiation when I was on a business trip to the town next to Three Mile Island during the accident in 1980.

Back when I was diagnosed, there was no standard treatment for multiple myeloma. My local hospital first put me on vincristine, doxorubicin (Adriamycin), and dexamethasone. But that chemotherapy regimen gave me serious heart problems, and after a month, they switched me to cyclophosphamide.

I was so sick that in May, the doctors told me I would be dead by Thanksgiving.

I was not satisfied with that answer and began looking for a second opinion. I ended up seeing Dr. Ken Anderson at Dana-Farber Cancer Institute. Dr. Anderson gave me a 5-year plan and told me, "If we can't cure you, we'll come up with the next best thing to keep you going until we find something that will give us a positive result."

I had a stem cell transplant on November 13, 1998. The high-dose chemotherapy and total-body radiation that preceded the transplant were brutal. My immune system was decimated, and I had to have all my routine childhood vaccinations again to rebuild my immune system. Life was extremely tough for 3 years, but I'm glad I did it.

After that, the only treatment I received until 2010 was thalidomide, in 1999, for some lytic bone lesions in my shoulder and pamidronate (Aredia) to strengthen my bones.

Then, in 2010, when I was helping out one of the patients that Dr. Anderson had asked me to mentor by driving him to Dana-Farber for treatment, I thought it would be a good time to have my blood checked because I had not had it done for a couple of years. Three days later, the doctor, Dr. Paul Richardson, called and said, "We have a problem."

I was back where I had started, with stage 3 multiple myeloma.

Dr. Richardson told me that treatment had changed a lot since my initial diagnosis and suggested I consider a clinical trial for an immunotherapy called elotuzumab. He explained that the drug would use my immune system to kill the cancer cells and that it was nothing like the radiation, chemotherapy, or stem cell transplant I had previously received. I trusted him implicitly and enrolled in the trial.

For the first 2 years, my M-spike, which is how the doctors keep track of how my disease is responding to treatment, kept going up and down. Then, in 2012, Dr. Richardson added intravenous immunoglobulin to my treatment plan, and my M-spike started falling. Last summer, it was so low that they did a bone marrow biopsy to see what was going on. They couldn't find any trace of cancer.

I'm currently taking a break from 73 months of treatment with elotuzumab, lenalidomide, and dexamethasone to give my body a rest. My M-spike numbers are staying low, and it seems that elotuzumab really did get my immune system to kill off the cancer cells.

I consider myself very blessed in so many ways and I want to give back. When I was diagnosed with multiple myeloma, the only person I had heard of who had the disease was Lenny Zakim. So I was delighted when Dr. Anderson asked me to be a mentor to other patients. It has given me a chance to help others navigate the disease. We have the tools to treat this devastating disease and give patients a better quality of life, as well as the realization that the diagnosis of multiple myeloma is no longer a death sentence.

IT IS ESTIMATED THAT 30,330 NEW CASES OF **MULTIPLE MYELOMA** WILL BE DIAGNOSED IN THE UNITED STATES IN 2016

© Glenn Kulbako


I consider myself very blessed in so many ways and I want to give back.

LIVING WITH CONFIDENCE AFTER MELANOMA THANKS TO T-VEC

BOB RIBBANS // AGE 67 // RINGOES, NEW JERSEY

At the end of 2009, when my melanoma spread to new areas of my skin, I felt like I was out of options. But my wife refused to give up and found out about a clinical trial testing a new type of treatment, an immunotherapy that is injected into individual melanoma lesions. I jumped at the chance to enroll in the trial, and thankfully, it was a success for me. As far as I'm concerned, I'm cured. I feel so confident that I'm hoping to be around to hold my great-grandchildren in my arms; my grandsons are still only 13 and 10.

I have spent most of my life outdoors. I was in the golf course industry for 36 years and worked on our farm in my spare time and since my retirement in 2006. I never wore a hat, and I'm sure that is one reason why I developed melanoma. Since my diagnosis, I always wear a hat and take great care to protect my skin from the sun.

It all started in the summer of 2008 when I noticed a scab on the top of my head. It wouldn't go away, so my wife encouraged me to see a dermatologist. I had a biopsy done at my first appointment, and it was just days later that I got a call from the dermatologist who told me that I had melanoma.

I didn't know much about melanoma—I knew it was skin cancer, but that was all. I immediately started looking on the internet for the cure for melanoma. I couldn't find one, and that was when I realized how serious things were.

My wife and I looked at my options, and we decided together that I would go to Memorial Sloan Kettering Cancer Center in New York for treatment. I had surgery to remove the melanoma lesions on my head and the surrounding skin. During the surgery, they removed an area of skin that was about 4 inches in diameter, but they covered that with a skin graft taken from the inner part of my left thigh.

Less than a year later, some melanoma lesions appeared inside the skin graft. Surgery was not an option, so I had radiation treatment. I went three times over a 6-week period. The lesions disappeared.

Six months later, however, four melanoma lesions appeared on my forehead, outside the area of radiation.

At this point, the doctor told me there were no localized treatment options; chemotherapy was my only choice. Fortunately, my wife, who works in the area of drug approvals, learned about a clinical trial at St. Luke's University Hospital in Bethlehem, Pennsylvania, through a business acquaintance. The trial was testing a new local treatment for melanoma called T-Vec (Imlygic).

We immediately made an appointment with the doctor at St. Luke's, and 3 weeks later, by which time two more lesions had appeared, I received my first treatment with T-Vec. I went for treatment every 2 weeks from January 2010 to April 2010. Each time, the T-Vec was injected directly into each melanoma lesion. At the end of that time, all of the lesions had disappeared.

One reason I am confident that my treatment with T-Vec was successful is that about 2 months after my final injections, I felt a lump on my neck the size of a dime. It was a lymph node, and a biopsy showed that although there were some viable melanoma cells present, most of the melanoma cells present were dead.

The T-Vec injected into the lesions in my skin had activated my immune system such that it could attack the melanoma in my lymph node. Erring on the side of caution, my doctors suggested I have several injections of T-Vec into the melanoma lesions in my lymph node. When a follow-up biopsy found all the melanoma cells were dead, I had the lymph node surgically removed.

Since then, I've been free of melanoma. I do have CT scans every 6 months and see my local dermatologist and the dermatologist at St. Luke's every 6 months, but my health is good. I feel very blessed to be around and credit the incredible support from my wife. During my experience, she was a huge pillar to lean on. She had every confidence in the world that T-Vec was going to work, and it has. I couldn't be more thankful for her support or more grateful for the research and clinical trial that led me to T-Vec because without it, I would not be here.

THE NUMBER OF NEW **MELANOMA** CASES DIAGNOSED EACH YEAR IN THE U.S. WILL RISE FROM 65,647 IN 2011 TO 112,000 IN 2030 IF CURRENT TRENDS CONTINUE

© Vera LaMarche

"I couldn't be more ... grateful for the research and clinical trial that led me to T-Vec, because without it, I would not be here."

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 (170):

choosing a physician(s) and treatment facility;

choosing among a variety of treatment options; and

managing 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 (170):

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

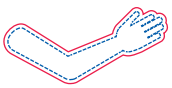
fear of cancer recurrence;

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, some segments of the population experience more than others (see sidebar on Surviving a Cancer Diagnosis as a Child or Adolescent, p. 97).

Adapted from (1)

Optimizing Quality of Life Across the Continuum of Cancer Care

In recent years, numerous changes have been made across the continuum of cancer care in an effort to improve the quality of life of people who are receiving cancer treatment or living long term with no evidence of disease. Many efforts have focused on reducing the risk of long-term and late effects of treatment, and a recent study found that these changes are bearing fruit for survivors of cancer diagnosed in childhood (173). The researchers found that far fewer survivors were dying as a result of late effects of cancer treatment, such as a second cancer or heart disease, compared with 3 decades ago.

Among the changes in treatment that are helping to reduce the short-term effects of treatment as well as the long-term and late effects of treatment, and thereby improve quality of life for the duration of the patient's life, is the increasing development and use of molecularly targeted therapeutics (see **Treatment With Molecularly Targeted Therapeutics**, p. 67). Because these anticancer therapeutics more precisely target a patient's cancer compared with cytotoxic chemotherapeutics, this has helped reduce the adverse effects of treatment for some patients.

Researchers are also looking for ways to increase the precision with which we use radiotherapy and cytotoxic chemotherapy to achieve maximal patient benefit with minimal harm. One promising approach is to use genomics to more precisely distinguish those patients with a given type of cancer who need aggressive treatment from those who would not gain benefit from it. To this end, in one recent phase III clinical trial, the use of a 70-gene signature MammaPrint genetic test identified 46 percent of a group of patients with early-stage breast cancer traditionally classed as at high risk for disease recurrence as unlikely to benefit from adjuvant cytotoxic chemotherapy (cytotoxic chemotherapy given after surgery) (173). In this case, the use of a genetic test has the potential to spare many patients from an aggressive treatment they will not benefit from.

One approach that can be used across the continuum of cancer care to improve the quality of life for patients and their families is palliative care (see sidebar on **Palliative Care**, p. 98). 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. Thus, palliative care specialists are trained to manage patient concerns such as anxiety, pain, nausea, vomiting, fatigue, difficulty sleeping, loss of appetite, and how to navigate the health care system.

About
3%
of cancer survivors in the United States received their cancer diagnosis as a child or adolescent (ages 0–19) (18).

SURVIVING A CANCER DIAGNOSIS AS A CHILD OR ADOLESCENT

380,000 Almost 380,000 survivors of cancer diagnosed by the age of 19, when they were a child or adolescent, were alive on Jan. 1, 2010 (18). Individuals in this group face long-term physical and emotional health challenges. For example:

98% 98 percent of adult survivors of childhood cancer have one or more chronic health conditions and 68 percent have severe/disabling or life-threatening conditions (171).

5% 5 percent of survivors of a cancer diagnosed in childhood develop a second cancer between 5 and 30 years after their initial diagnosis (172).

The Children's Oncology Group "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 a child, adolescent, or young adult. For more information, see http://survivorshipguidelines.org/.

Adapted from (24)

Research shows that in addition to increasing quality of life, providing palliative care administered by a specialist palliative care team to patients who are being treated for cancer can also improve survival and that the sooner palliative is initiated after a cancer diagnosis, the more patients benefit (175, 176). Moreover, a recent study found that family caregivers of cancer patients who received palliative care had a better quality of life and fewer symptoms of depression compared with family caregivers of those patients who did not receive palliative care (176).

Despite the growing evidence that specialist palliative care has tremendous benefits for patients with cancer and their families, there is a need for additional carefully designed clinical trials to more clearly determine the best time to initiate palliative care after a cancer diagnosis and the best way to deliver the care to achieve the maximum benefit for patients and their families (177). Two ongoing randomized clinical trials, which recently reported early data indicating that integrating specialist palliative care during the early stages of cancer care improved quality of life, should help

WHAT IS PALLIATIVE CARE?

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

WHO PROVIDES PALLIATIVE CARE?

Any health care provider can provide primary palliative care by addressing the adverse effects and emotional issues facing a patient with cancer, but some specialize in this area of patient care.

Palliative care specialists usually work as part of multidisciplinary team that includes doctors, nurses, registered dieticians, pharmacists, social workers, psychologists, and chaplains.

The palliative care team works alongside the physicians treating the patient's cancer.

WHO CAN RECEIVE PALLIATIVE CARE?

Any patient diagnosed with a serious illness, such as cancer, including children.

The family members and friends of a patient diagnosed with a serious illness can receive palliative care to help provide them the support they need.

WHERE CAN PATIENTS RECEIVE PALLIATIVE CARE?

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

provide insight in this regard (179, 180). Moreover, it is imperative that we increase awareness among both the general public and health care providers of the important role that palliative care can play across the continuum of clinical cancer care, because there are still many patients who do not receive palliative care or even know what it is (180).

Hair loss is one adverse effect of treatment with many cytotoxic chemotherapeutics that has been reported to negatively affect quality of life, especially for women with breast cancer (181). In December 2015, the FDA approved a medical device to help address this quality of life issue for women being treated with cytotoxic chemotherapeutics after a breast cancer diagnosis. The device, which is called the Dignitana DigniCap 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 to be effective at reducing hair loss in numerous clinical trials (183).

Some forms of complementary and alternative medicine have been shown to improve quality of life for patients with cancer. For example, studies have shown that yoga, yoga breathing, acupuncture, and ginger reduce certain adverse effects of chemotherapy and radiotherapy, including fatigue, nausea, sleep disturbance, anxiety, and joint pain (184-187). In addition, relaxing acupressure was recently shown in a large randomized clinical trial to reduce fatigue and improve sleep quality and quality of life among patients with breast cancer who had completed cancer treatment (187). Other forms of complementary and alternative medicine have not been well studied, so we do not know if they are safe or effective. Despite this, a recent study showed that U.S. out-of-pocket spending on complementary health approaches reached $30.2 billion in 2012 (188). Thus, it is clear that there is an urgent need for more research in this area.

Modifying Behaviors to Improve Outcomes

A major concern for all cancer survivors who successfully complete their initial treatment is whether their cancer will return or cause their death. 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 3**, p. 24). Thus, modifying behaviors to eliminate or avoid these risk factors can improve outcomes and quality of life for cancer survivors.

For example, research shows that quitting smoking can improve outcomes for cancer survivors: it reduces risk of death from cancer, and it also reduces risk for developing a second cancer (34). Even in the face of this knowledge, a recent study found that 9 percent of cancer survivors continue to smoke (190). Therefore, enhanced provision of cessation assistance to all patients with cancer who use tobacco or who have recently quit smoking is urgently needed, as is further research to improve our understanding of how best to help individuals quit (191).

According to the NCI:

Complementary medicine

refers to treatments that are used alongside standard medical treatments, but they are not themselves considered standard treatments, for example, using acupuncture to help reduce some of the adverse effects of cancer treatment.

Alternative medicine

refers to treatments that are used in place of standard medical treatments.

In addition to adversely affecting outcomes for patients with cancer, tobacco use is an important source of variation in cancer treatment clinical trials (191). Despite the fact that tobacco use has the potential to affect both how a patient might respond to the treatment being tested and the ability of researchers to interpret the results of the trial, a trial participant's tobacco use and possible exposure to secondhand smoke are often not recorded. To address this issue, researchers have developed a new tool that they hope will be routinely used by clinical trialists to help us gain a clearer understanding of the significance of tobacco use and cessation in clinical trials and for cancer patients more broadly (191).

Evidence is also beginning to emerge that regular aerobic exercise can reduce recurrence and mortality in survivors of early breast, prostate, and colorectal cancers (192). More recently, clinical trial results showed that breast cancer survivors who participated in a weight training program had increased muscle strength and experienced less deterioration of physical function (194, 195). This finding is important because deterioration of physical function and loss of muscle strength have been linked to increased risk for bone fractures and other health issues that limit quality of life. However, more research is required to confirm these observations and fully understand whether and how changes in physical activity after diagnosis might affect outcomes.

ANTICIPATING FUTURE PROGRESS

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.
- Research, in particular cancer genomics research, will continue to revolutionize cancer treatment, including expanding the more precise use of existing therapies.
- Developing an even more comprehensive, whole-patient understanding of cancer will accelerate the pace of progress toward precision cancer prevention.

We have made significant advances against cancer, with many more people living longer and leading fuller lives after a cancer diagnosis than ever before. Even with this progress, however, it is estimated that in 2016 alone, more than 1.68 million U.S. residents will receive a cancer diagnosis, and more than 595,000 will die from the disease (3).

Computational biology is the development and application of data-analytical and theoretical methods, mathematical modeling, and computational simulation techniques to the study of biological, behavioral, and social systems (195).

Bioinformatics is the research, development, or application of computational tools and approaches for expanding the use of biological, medical, behavioral, or health data, including those to acquire, store, organize, archive, analyze, or visualize such data (195).

Despite this enormous burden of cancer, many researchers, including AACR President (2016–2017) **Nancy E. Davidson, MD** (see p. 102), think the future is bright and that through research, we will be able to power more advances against cancer.

Research is the foundation on which progress against cancer has been and continues to be made. We have found that the more we know about the biology of cancer and about an individual, the more precisely we are able to prevent, detect, diagnose, and treat cancer for that person. Thus, it is clear that more research that provides us with an even more comprehensive understanding of the biology of cancer and its causes is required if we are to make future lifesaving progress.

Recently, discoveries in the fields of cancer genomics and immunology have been particularly fruitful and have firmly established two new pillars of cancer care: precision therapy and immunotherapy. These exciting fields of research also show immense promise for the future because the pace of progress in these areas is expected to accelerate further.

As discussed in **Biomedical Research** (see p. 48), however, if we are to efficiently analyze and use the explosion of information generated by cancer genomics research to identify new therapeutic targets and novel genomic signatures of therapeutic response or prognosis, it will be essential to more fully engage computational biology and bioinformatics researchers who can help convert these data into knowledge. Additionally, further progress will be made by rapidly developing and incorporating new research technologies across the entire biomedical research cycle (see sidebar on **CRISPR 101**, p. 101).

One use of cancer genomics research is to identify genomic signatures that identify which patients are likely to respond to a particular treatment. One area where this holds immense promise is immunotherapy (see **Treatment With Immunotherapeutics**, p. 81), in particular, the use of immunotherapeutics that work by releasing the brakes on the immune system, where markers predictive of response have been challenging to identify. One study highlighting the exciting potential of this approach showed that the presence of certain genetic mutations in colorectal cancers predicted response to pembrolizumab (164) and led to the FDA granting pembrolizumab breakthrough therapy designation for use in these patients. Several other studies have used large-scale genomics to identify genetic signatures of melanoma response to ipilimumab (198, 199), although these are early studies that need further validation before the results can be translated into the clinic.

Cancer genomics is not the only research discipline that has the potential to pinpoint new markers that identify which patients are likely to respond to a particular treatment. A number of preclinical studies have shown that the bacterial species in the intestinal microbiota—the microbes that naturally colonize the intestines—of mice influences the anticancer efficacy of cytotoxic chemotherapeutics and immunotherapeutics (200, 201). Whether the intestinal microbiota have similar effects on the efficacy of anticancer therapeutics in humans has yet to be determined, but if it does, it raises the possibility that manipulating a patient's microbiota may modulate the response of his or her cancer to some types of treatment.

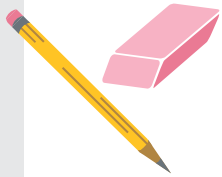
Preclinical research has also shown that one way in which the intestinal microbiota can influence the immune system in mice is through the metabolites produced by the bacteria (202). Metabolites are the breakdown products of larger nutrient molecules. Thus, metabolomics, which is the simultaneous study of as many metabolites in a biological system of interest as possible, such as the blood, urine or a tissue sample, is an area of interest as researchers look for clues to understanding how the intestinal microbiota might influence the response to anticancer therapeutics.

Because the way in which normal cells and tumor cells convert or use energy is often different, metabolomics also has the potential to improve our understanding of cancer biology; to identify markers for cancer detection, diagnosis, and monitoring of treatment response; and to open new avenues of investigation for cancer prevention, detection, diagnosis, and treatment (203).

As our knowledge of cancer biology grows, it is becoming increasingly clear that we cannot study cancer in isolation. We need to know more about the whole person in which the cancer has developed. Nowhere is this more apparent than in the emerging area of precision prevention (see **Figure 2**, p. 22). Precision prevention is a conceptual framework that aims to tailor cancer prevention to the individual patient by accounting for the various factors that may play a role in developing a particular cancer (26). As we develop an even more comprehensive, whole-patient understanding of the way in which cancer starts, progresses, and results in disease, we can expect to see an acceleration in the pace of progress in precision cancer prevention.

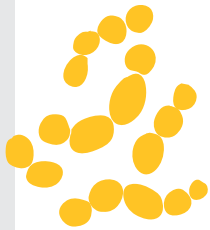
CRISPR 101

Investigating the effects of changing, or editing, the genetic material of a cell is an important part of biomedical research. It is particularly vital during the discovery phase of biomedical research and in therapeutic development (see Figure 9, p. 49).



CRISPR is a revolutionary approach to gene editing that has emerged in the past 2 or 3 years (197).

It provides a faster and more precise and efficient approach to gene editing compared with previous technologies.



The development of CRISPR technology was based on research into the immune system of certain species of bacteria.

CRISPR technology is being used by researchers throughout the biomedical research community in numerous ways and is being investigated as a potential way to treat certain genetic diseases and to modify certain approaches to immunotherapy.

“This is an amazing time scientifically for us; the momentum couldn’t be greater.”

FUTURE PROGRESS WILL COME FROM NEW INSIGHTS ABOUT CANCER DISCOVERED BY A DIVERSE NEXT-GENERATION CANCER RESEARCH WORKFORCE

NANCY E. DAVIDSON, MD \\ AACR PRESIDENT, 2016–2017 \\
DIRECTOR, UNIVERSITY OF PITTSBURGH CANCER INSTITUTE, PITTSBURGH, PENNSYLVANIA

Over the course of my career, cancer mortality in the United States has dropped about 1 percent each year. It is impossible to identify one thing that has single-handedly contributed to this decrease in the burden of cancer. Rather, the inroads we have made are a result of advances across the spectrum of cancer research from genetic testing to targeted therapy to smoking cessation.

Everything we know today about how to take care of people with cancer is built on decades of research. Today's research is the foundation for tomorrow's standard therapy.

Research has led to so many improvements in treatment, including new systemic therapies, new targeted therapies, new immunotherapies, new surgical techniques, and new approaches to radiotherapy. All of these have been vital in reducing the burden of cancer.

Nor should we forget the importance of early detection and prevention strategies as simple as smoking cessation, which is the single most important action we can take to reduce the burden of cancer moving forward.

In cancer, I think that sometimes we have been accused of overpromising and underdelivering. This is something we must avoid. But I believe that if we took the fruits of our knowledge—what we know today—and put those into practice right now for all individuals across our globe, we would make an immediate and incredible impact on the burden of cancer.

Despite the great progress we have made against cancer, the number of people receiving a cancer diagnosis each year in the United States is expected to rise over the coming decades because of a growing and aging population. We must strive to do better for these individuals.

Going forward, it would be naïve of us to think that a single discovery is going to make all the difference because cancer is such a complex collection of diseases. Nonetheless, I think that over the next few years, we will see a continuing refinement of the way we use precision medicine to select targeted therapies, improve the way that we apply immunotherapy, and refine surgical and radiotherapeutic techniques. I am certain these areas will play a substantial role in cancer therapy over the next few years.

Over the long term, I truly believe that we are going to see the impact of early detection and cancer prevention strategies increase, and that we will be able to come to the point where we can enable the concept of personalized screening and personalized cancer prevention.

However, continued progress is going to require a sustained federal commitment to the research agenda. To that end, we are very grateful to President Obama and Vice President Biden for putting cancer and cancer research on the map again in the way that they have with the National Cancer Moonshot Initiative. This is an amazing time scientifically for us; the momentum couldn't be greater. So, we are delighted that they have been able to galvanize attention about the importance of cancer research. Of course, we hope that ultimately, this will translate into the crucial resources that are going to be required in order to make an even bigger difference against the complex diseases we call cancer.

It is my hope that the momentum created by the National Cancer Moonshot Initiative will energize today's cancer researchers and also galvanize early-career investigators to come into the field. It is clear that we will not solve the problem of cancer in the next several years. So, it is absolutely critical that we bring to bear our most important resource, early-career investigators from across all scientific disciplines with brilliant new ideas.

The AACR is committed to bringing to the forefront this next generation of cancer researchers, those who are basic scientists, computational scientists, translational scientists, clinical scientists, population scientists, implementation scientists, and more. This is because they reflect the full spectrum of research expertise that we will need to make the next big leaps against cancer.

BUILDING BLOCKS OF FURTHER PROGRESS AGAINST CANCER

In this section you will learn:

- Increasing federal support for biomedical research and cross-cutting research initiatives is crucial for furthering 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.
- Precision prevention and early detection have the potential to reduce the burden of cancer.

It is a transformational time in cancer research. As we have delved deeper into the complexity of cancer, we have experienced an explosion in our understanding of the individual factors both inside and outside a cell that cause cancer initiation, development, and progression. This knowledge is beginning to unveil a clearer picture of how these factors work together and are influenced by each person's unique biological characteristics.

Thanks to the efforts of countless researchers, physician-scientists, patient advocates, and other representatives from all sectors of the biomedical research community (see sidebar on **The Biomedical Research Community: Powering Progress Together**, p. 9), we are developing new methods for preventing, detecting, diagnosing, and treating cancer. More effective and less toxic interventions improve patient quality of life and ultimately, save more lives from cancer.

Between Aug. 1, 2015 and July 31, 2016, the FDA approved 18 new medical products for use in oncology—13 new anticancer therapeutics, one new cancer screening test, one new diagnostic test, two new diagnostic imaging agents, and a new medical device. During this same period, the FDA also approved new uses for 11 previously approved, anticancer therapeutics.

This progress would not have been possible without strong, bipartisan leadership and federal support for the NIH, NCI, and FDA and innovative programs, such as the Precision Medicine Initative (PMI). As the National Cancer Moonshot Initiative gets underway, it will be important that this promising effort receives support and robust funding as well (see sidebar on **Building Blocks of Further Progress Against Cancer**).

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 cross-cutting initiatives to advance progress against cancer.

Support regulatory science initiatives.

Develop and train the biomedical research workforce of tomorrow.

Support precision prevention efforts.

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 the majority of scientific and medical discoveries are made. In the 45 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 extraordinary progress against cancer, as detailed in this report.

A strong federal investment in cancer research is good, both for our nation's health and our economy. The impact of federal support for the NIH, NCI, and FDA reaches well beyond the laboratory and the clinic. More than 80 percent of the funds appropriated by Congress to the NIH are distributed to all 50 states and around the world to drive research, and it is estimated that every dollar invested in the NIH yields $2.21 in local economic growth. As a result, hundreds of thousands of jobs are created, and entirely new industries are established, such as the biotechnology industry.

As discussed by **Senator Roy Blunt** (see p. 106), a decade of stagnant budgets at the NIH led to a more than 20 percent decline in purchasing power and threatened the United States' position as the world leader in biomedical research. Recent funding increases signal an end to this troubling trend, but the budget must continue to grow at a level that outpaces inflation (see **Figure 17**, p. 108). This renewed investment in biomedical research will strengthen the position of the United States as the global leader in science and technology, and will ensure U.S. economic leadership in the 21st century.

SUPPORT FOR CROSS-CUTTING INITIATIVES TO ADVANCE PROGRESS AGAINST CANCER

As highlighted in **Anticipating Future Progress** (see p. 100), conquering a disease as complex as cancer requires a multidisciplinary approach, including collaborations with experts in areas of science, engineering, and technology that were not historically part of the cancer research ecosystem. Two examples of cross-cutting endeavors that are bringing many stakeholders together to advance progress against cancer are the National Cancer Moonshot Initiative and the Precision Medicine Initiative. These initiatives aim to bring various facets of the government, as well as the public and private sectors together to accelerate the pace of progress against disease, particularly cancer.

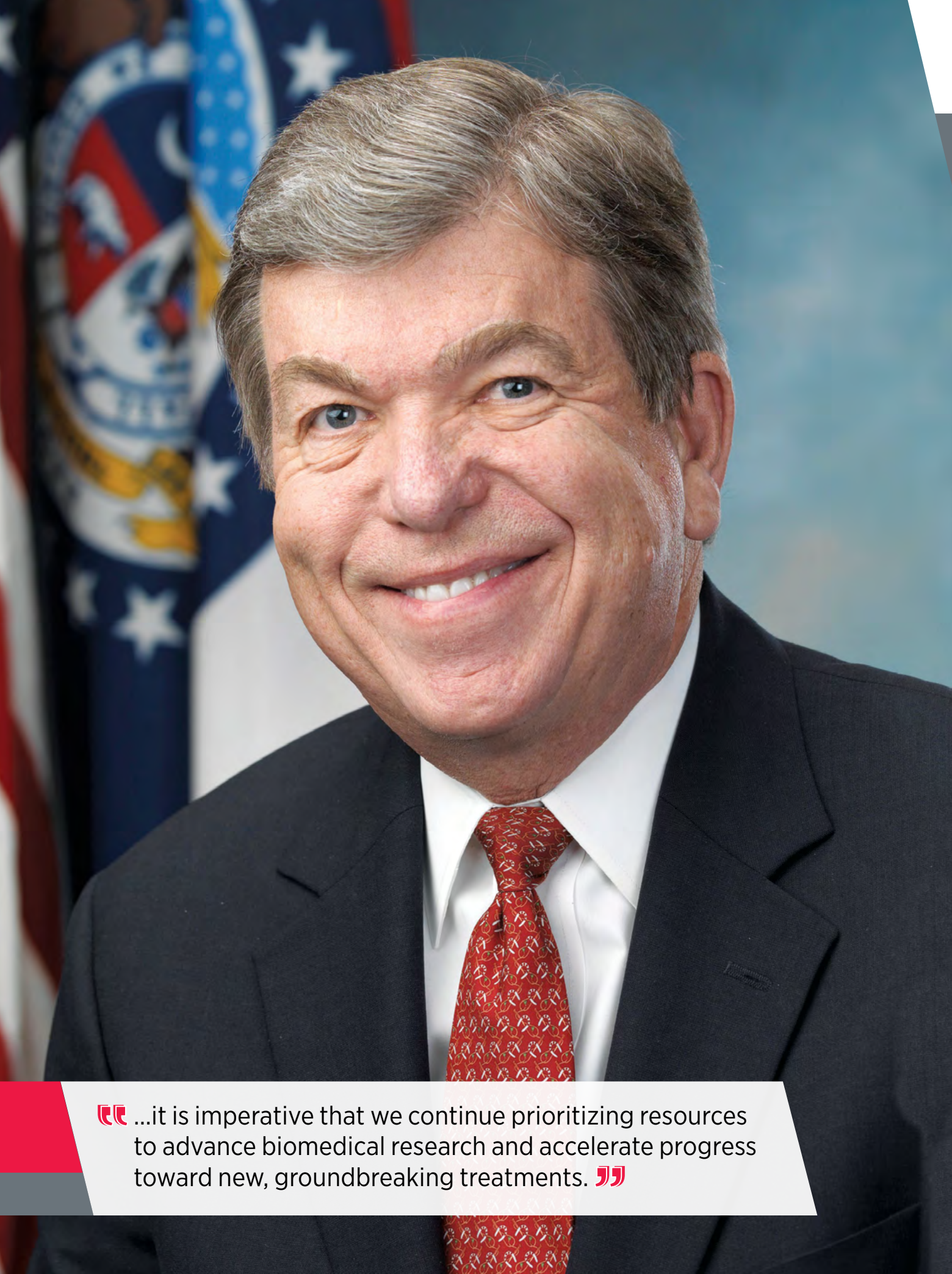
National Cancer Moonshot Initiative

During a speech in the White House Rose Garden on Oct. 21, 2015, where he was announcing that he would not run for President of the United States in 2016, Vice President Joe Biden referenced the tragic loss of his son to cancer and called for a "moonshot" to cure this terrible disease. The Vice President stated that we have a remarkable opportunity to advance many of the breakthroughs that are just on the horizon, provided that we join together to "make an absolute national commitment to end cancer, as we know it today." In his final State of the Union address, President Obama followed Biden's call with the announcement that he was tasking the Vice President with spearheading a national effort against cancer.

This extraordinary announcement was followed by the launch of the National Cancer Moonshot Initiative, which seeks to double the rate of progress toward a cure for cancer by achieving 10 years of progress in 5 years (see sidebar on **The National Cancer Moonshot Initiative**, p. 110). Since February 2016, the Vice President has created a federal interagency task force, bringing together every federal agency that has a role to play in addressing cancer. The Task Force is charged with producing recommendations before December 31, 2016, on how to accelerate the pace of progress across a number of areas—from cancer prevention and early detection, to patient access and care, to data and computational capabilities, to implementation science.

In April 2016, the Cancer Moonshot Blue Ribbon Panel was established to inform the scientific direction and goals at NCI of Vice President Biden's National Cancer Moonshot initiative (see sidebar on **The National Cancer Moonshot Initiative**, p. 110). The 28-member panel, comprised of cancer researchers, physician-scientists, oncologists, patient advocates, and representatives from the private sector and government agencies, serves as a working group of the presidentially appointed National Cancer Advisory Board (NCAB). The Panel is co-chaired by Tyler Jacks, PhD, Chair, National Cancer Advisory Board Director, Koch Institute for Integrative Cancer Research, Massachusetts Institute of Technology ; Elizabeth Jaffee, MD, Professor and Deputy Director for Translational Research, Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins University School of Medicine; and Dinah Singer, PhD, Acting Deputy Director, National Cancer Institute, Director, Division of Cancer Biology, National Cancer Institute.

The FDA will also play an integral role in the implementation of the initiative. Towards this end, the FDA Oncology Center of Excellence (OCE) (see sidebar on **FDA Oncology Center of Excellence**, p.108) was established. The OCE aims to expedite the development of novel combination products and support an integrated approach to tackling cancer.



"...it is imperative that we continue prioritizing resources to advance biomedical research and accelerate progress toward new, groundbreaking treatments."

CANCER AFFECTS US ALL

THE HONORABLE ROY BLUNT \\ U.S. SENATOR FOR MISSOURI \\ CHAIRMAN OF THE SENATE APPROPRIATIONS SUBCOMMITTEE ON LABOR, HEALTH AND HUMAN SERVICES, EDUCATION, AND RELATED AGENCIES. \\ AGE 66

RENAL AND **PROSTATE** CANCER SURVIVOR

When your family is healthy, you have many problems; when someone in your family is sick, you have only one problem. That's especially true for any family that has faced a cancer diagnosis. In 2016, nearly 1.7 million Americans are expected to be diagnosed with cancer for the first time, and nearly 600,000 will lose their lives to the disease, according to the American Cancer Society. That's why it is imperative that we continue prioritizing resources to advance biomedical research and accelerate progress toward new, groundbreaking treatments.

As chairman of the U.S. Senate Appropriations Subcommittee on Labor, Health and Human Services (HHS), I was proud to write and pass a funding bill last year that raised the National Institutes of Health's funding by $2 billion, a 6.7 percent increase. This amount represented the largest funding increase the NIH received in this bill in over a decade. I'm glad to announce we're on track to provide another $2 billion increase this year as part of the first bipartisan Senate Labor/HHS appropriations bill in 7 years. This year's bill, which was reported by the Appropriations Committee in June, includes more than $5.4 billion for the National Cancer Institute (NCI), a 4 percent increase. Coupled with last year's funding, that represents a 9.6 percent increase over the past 2 years for the NCI. We achieved that increase, in part, by eliminating 36 ineffective or duplicative programs.

Together, the NIH and NCI are paving the way for the next breakthrough in cancer research. As a renal and prostate cancer survivor, I'm particularly interested in the progress that's underway in the field of precision medicine. Last year, we began a new Precision Medicine Initiative, which utilizes specific genetic, environmental, and lifestyle data to tailor treatments to individuals. As Dr. Douglas Lowy, the acting director at NCI, explained at a recent hearing before the Labor/HHS Appropriations Subcommittee, this type of research is critical for determining how "you deliver the right drug, to the right patient, at the right time."

For example, a recent clinical trial for a genetic test known as MammaPrint found that as many as half of the patients who were slated for chemotherapy based on traditional clinical assessments did not actually require the treatment. According to the study, patients with breast cancer who underwent surgery to remove their tumors and had a MammaPrint score recommending against chemotherapy, had a 95 percent survival rate. The study confirms what I heard from doctors and researchers at the Siteman Cancer Center in St. Louis earlier this year, who told me that developing targeted therapies through precision medicine has the potential to save patients unnecessary—and often aggressive—treatmentwhile driving down health care costs.

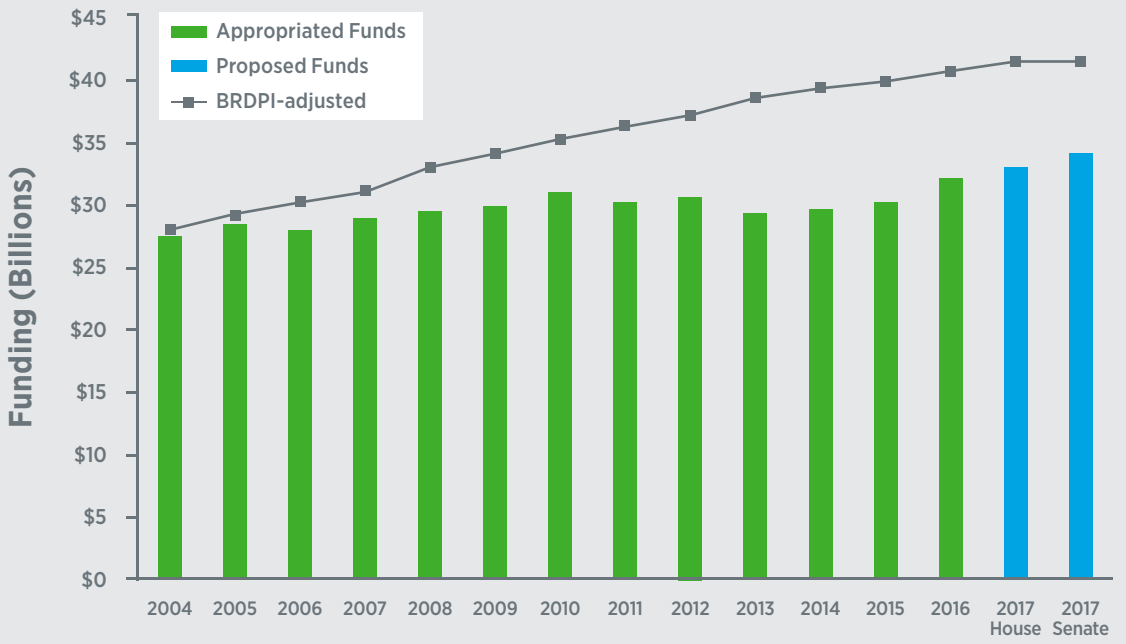
Federal funding for cancer research and prevention has historically driven major breakthroughs in the field and will continue to play a pivotal role. The investments we make today will not only save lives, but they'll also lead to new frontiers in drug and device development that are critical for reducing health care costs, growing our economy, and maintaining America's competitive edge in innovation.

Over the past decade, the NIH has lost more than 20 percent of its research purchasing power. I'm proud that we were able to take a step toward bridging that gap last year. I will continue making NIH and cancer research funding a priority in the fiscal year ahead, in the hopes that we can sustain an upward trajectory in biomedical investment within the constraints of a tough fiscal environment.

In my view, every dollar we spend should reflect the priorities of the American people. I can think of no greater priority than to give hope to families battling cancer and to help more people live longer, healthier lives. I'm incredibly grateful for the treatment I received and the researchers and doctors who made my recovery possible. I will continue fighting to give all Americans the same opportunity.

FIGURE 17

TURNING A CORNER



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. However, the gap is closing as a funding increase of $2 billion in fiscal year (FY) 2016 provided real growth in excess of inflation. Additional increases proposed for FY 2017 are helping us continue to turn the corner after the decade of stagnant investment (see blue bars).

FDA ONCOLOGY CENTER OF EXCELLENCE

On June 29, 2016, U.S. Food and Drug Administration (FDA) Commissioner Robert Califf announced the creation of a new Oncology Center of Excellence (OCE) at the FDA, and he appointed Richard Pazdur, MD, as acting director. This new center, which will play a key role in advancing the National Cancer Moonshot Initiative, will leverage the combined skills of regulatory scientists and reviewers with expertise in drugs, biologics, and devices to expedite the development of novel combination products for the benefit of patients with cancer. The new FDA OCE will bring staff from all the important areas of the cancer drug development process together to fuel the progress we are seeing today in preventing, detecting, and treating cancer.

The Precision Medicine Initiative

The Precision Medicine Initiative (PMI) was unveiled by President Barack Obama in January 2015. The goal of the PMI is to build on advances in precision oncology and extend precision medicine treatments to all forms of cancer and many other diseases.

Of the $300 million assigned to the PMI in the FY 2016 budget, $70 million were directed to the NCI to scale up efforts to identify genomic drivers of cancer and apply that knowledge in the development of more effective approaches to cancer treatment.

One area of particular focus is expanding precision medicine clinical trials, with an emphasis on supporting the NCI-Molecular Analysis for Therapy Choice (MATCH) clinical trial and planning and conducting a trial that will be known as NCI Pediatric MATCH. Other areas of focus include exploring fundamental aspects of cancer biology, and establishing a national "cancer knowledge network" to generate and share new knowledge to fuel scientific discovery and guide treatment decisions.

ENHANCED SUPPORT FOR REGULATORY SCIENCE AND POLICY AT THE FDA

The FDA is an integral part of the biomedical research community, and the support of this critical agency through robust, annual appropriations from Congress is crucial if we are to continue to make progress against cancer through the delivery of safe, effective, and increasingly precise therapies to patients. The advancement of regulatory science, which is the study of developing new tools, standards, and approaches to assess the safety, efficacy, quality, validity, and performance of medical products, is especially important. The regulatory science initiatives of the FDA are aimed at promoting and developing evidence-based regulatory policies that balance innovation and the expedited approval of medical products with patient safety. These activities are not supported through user fees, but rather, depend on annual funding from Congress.

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 the government. Therefore, Congress must continue to equip the agency the resources it needs to support these regulatory processes, professional development of staff, and expand hiring authority.

DEVELOPING AND TRAINING THE WORKFORCE OF TOMORROW

Many of the most innovative research questions and fresh ideas come from scientists early in their careers. Ensuring the pace of progress against cancer continues requires that the next generation of cancer researchers be recruited, supported and encouraged. A strong pipeline of talented researchers to whom current leaders in the field can pass the baton in the years to come will allow the work to continue in 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 have come of age in a decade when research funds were scarce, federal research budgets declined by more than 20 percent when adjusted for inflation, and the path forward was uncertain. Because of the difficult funding environment in recent years, many young investigators have opted for alternative career paths, thereby putting future generations of innovative research in jeopardy.

Our country must continue to invest in education and training of scientists at all career levels, but especially in 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 federal, state, and private sector-funded programs to assist early-career scientists, play an irreplaceable role in attracting and retaining tomorrow's scientific leaders.

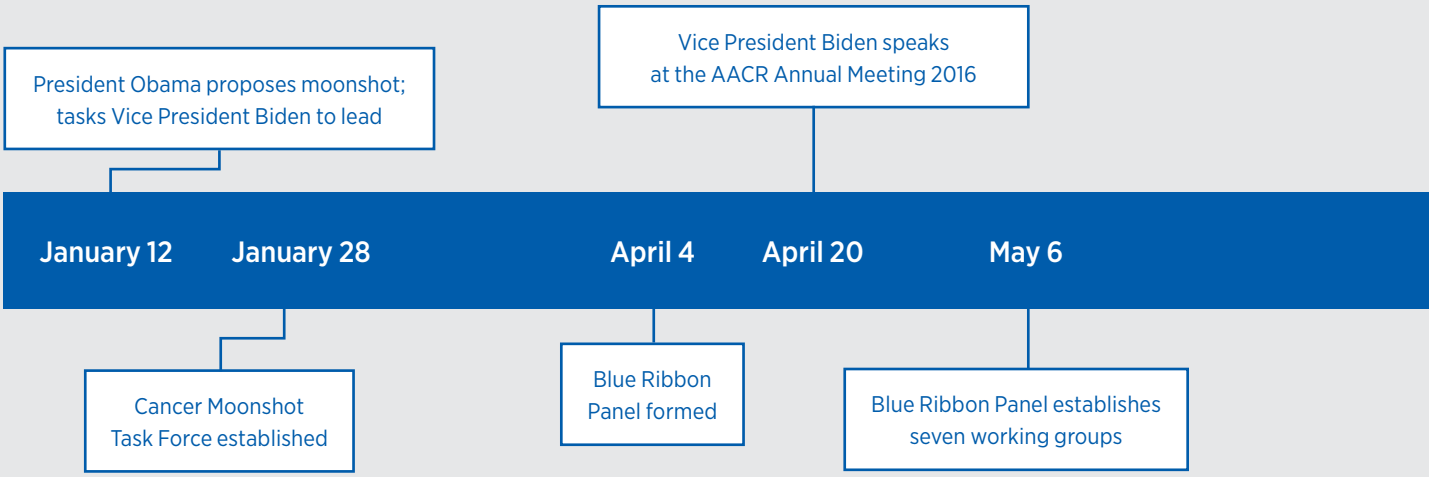
PRECISION PREVENTION AND EARLY DETECTION

We know that more than half of global cancer cases are a result of preventable causes and that prevention is perhaps the most cost-effective strategy for controlling cancer in the long run. Thus, an increased focus on cancer prevention and early detection is required if we are to decrease cancer incidence, morbidity, mortality, and cost worldwide.

Thanks to the wealth of research demonstrating the health consequences of tobacco use, we have seen dramatic progress in the area of tobacco control through the implementation of policies and educational initiatives aimed at preventing use and facilitating cessation. As electronic nicotine delivery systems (ENDS), commonly called e-cigarettes, have proliferated in recent years, the need to understand and balance the

THE NATIONAL CANCER MOONSHOT INITIATIVE

The National Cancer Moonshot Initiative seeks to double the rate of progress toward a cure for cancer by achieving 10 years of progress in 5 years. The initiative is led by Vice President Joe Biden and a federal interagency task force. A Blue Ribbon Panel, and its seven working groups, provide scientific advice to the Task Force.



BLUE RIBBON PANEL

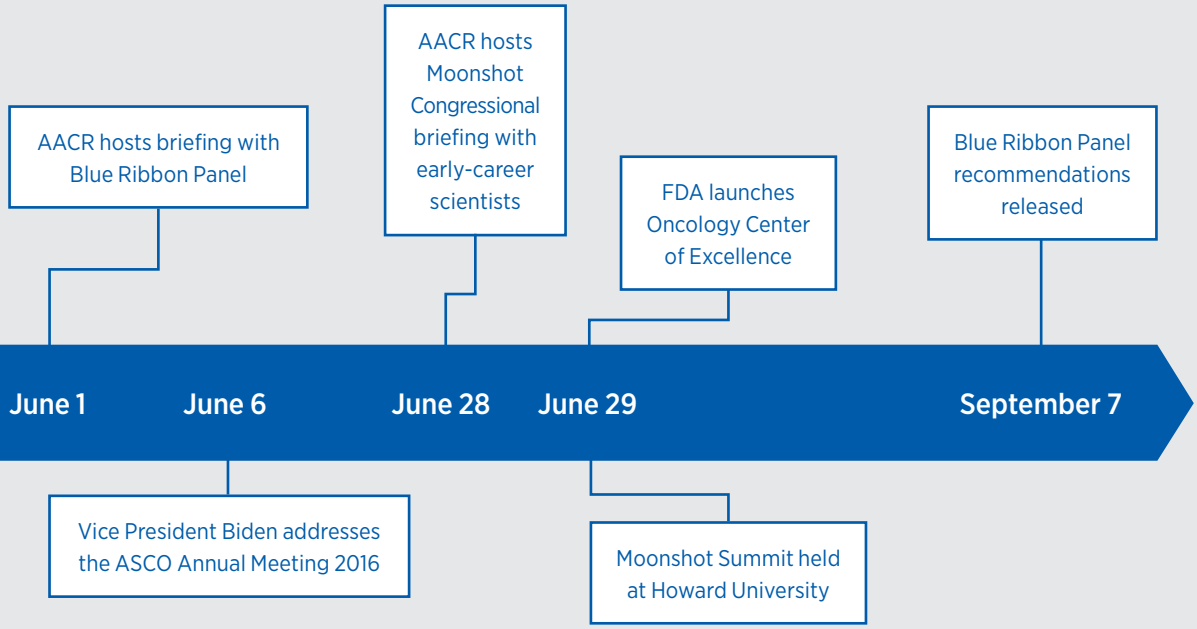
- Tyler Jacks, PhD (Co-Chair)
- Elizabeth M. Jaffee, MD (Co-Chair)
- Dinah S. Singer, PhD (Co-Chair)
- Peter C. Adamson, MD
- James P. Allison, PhD
- David F. Arons, JD
- Mary C. Beckerle, PhD
- Mitchel S. Berger, MD
- Jeffrey A. Bluestone, PhD
- Chi Van Dang, MD, PhD
- Mikael Dolsten, MD, PhD
- James R. Downing, MD
- Levi A. Garraway, MD, PhD
- Gad Getz, PhD
- Laurie H. Glimcher, MD
- Lifang Hou, MD, PhD
- Neal Kassell, MD
- María Elena Martínez, PhD
- Deborah Mayer, PhD, RN
- Edith P. Mitchell, MD, FAC
- Augusto C. Ochoa, MD
- Jennifer A. Pietenpol, PhD
- Angel Pizarro, MSE
- Barbara K. Rimer, DrPH
- Charles L. Sawyers, MD
- Ellen V. Sigal, PhD
- Patrick Soon-Shiong, MD, FRCS (C), FACS
- Wai-Kwan Alfred Yung, MD

7

working groups developed recommendations and evaluated others from the community and the public.

EX OFFICIO MEMBERS OF THE BLUE RIBBON PANEL ARE:

- David Atkins, MD, MPH
- Robert M. Califf, MD
- Karen S. Guice, MD, MPP
- Jason Paragas, PhD
- Lawrence A. Tabak, DDS, PhD



BLUE RIBBON PANEL RECOMMENDATIONS

1. **Network for direct patient engagement**
Encourages patients to have their tumor genome sequenced, automatically shares the results through a network of linked databases, and enables clinical trial enrollment when appropriate.

2. **Cancer immunotherapy clinical trials network**
A network of clinical trials in adult and pediatric patients to evaluate immunotherapies and vaccines.

3. **Therapeutic target identification to overcome drug resistance**
Methods to identify mechanisms of drug resistance and develop therapeutic strategies to prevent and overcome it.

4. **A national cancer data ecosystem for sharing and analysis**
Develops the computational and bioinformatic infrastructure necessary to share any kind of data with anyone while maintaining privacy and security.

5. **Fusion oncoproteins in pediatric cancer**
Develop new therapeutics targeting pediatric fusion proteins through the use of new research models.

6. **Symptom management research**
Use patient reported outcomes to develop evidence-based guidelines to manage patient symptoms throughout the course of clinical care.

7. **Prevention and early detection: implementation of evidence-based approaches**
Use research to discover, test, and implement strategies to reduce cancer risk, with an initial focus on fully executing established risk-reduction strategies.

8. **Retrospective analysis of biospecimens from patients treated with standard of care**
Analyze existing and future samples from patients receiving standard of care to enable the precise use of standard treatments and catalyze additional research.

9. **Generation of human tumor atlases**
Develop comprehensive maps of all of the alterations within as many different tumors as possible to fully enable precision medicine.

10. **Development of new enabling cancer technologies**
The new technologies will be used to enable further discoveries and improve patient care.

potential cessation benefits and health risks associated with use of these products has grown (see sidebar on **E-cigarettes: What We Know and What We Need to Know**, p. 27). Recently, the FDA announced it would take the important step of regulating these tobacco-derived products and increase efforts to keep them out of the hands of youth (see sidebar on **Enhancing Tobacco Control Through FDA Regulation**, p. 28).

As discussed in **Protect Skin From UV Exposure**, p. 32, skin cancer prevention also remains a critical issue where significant, additional progress can be made. There is a growing body of scientific evidence that shows indoor tanning dramatically increases a person's risk of skin cancer, including melanoma (65). In fact, one study found that individuals who have been exposed to UV radiation from indoor tanning before the age of 35 are 59 percent more likely to develop melanoma than those who have never tanned indoors (203). In an effort to strengthen policies in this area, the FDA issued a proposed rule in 2016 to prohibit the use of tanning beds by those under age 18 (see sidebar on **Indoor Tanning Legislation**, p. 32).

Increasingly, scientists are applying the principles of precision medicine to prevention, and this is a rapidly growing area of research (see **Anticipating Future Progress**, p. 100). Advances in genomic technologies can lead to improved prevention and early detection strategies. As we develop a better understanding of common genetic variants associated with a higher or lower risk of certain cancers, we may be able to use that knowledge to identify individuals who may or may not benefit from particular prevention strategies.

With respect to early detection, precision medicine applications can enable noninvasive screening for very early cancers. Liquid biopsies, noninvasive tests performed on biofluids to detect genetic alterations in tumors, are a recent revolution in the oncology field, and the technology is continuing to advance rapidly. In fact, the first liquid biopsy test was approved by the FDA in June 2016 to identify patients with metastatic NSCLC eligible for treatment with the EGFR-targeted therapeutic erlotinib (see **Helping Some Lung Cancer Patients Breathe Easier**, p. 70). When successfully integrated into clinics, liquid biopsies have the potential to improve all aspects of clinical cancer care, including early detection.

Although liquid biopsies offer manifold possibilities for improving cancer care, as with any emerging technology, there are many practical and logistical challenges in taking this technology to the next level and making it a standard of care for patients with cancer.

Strong support for cancer prevention research, coupled with support for a regulatory environment that will support the translation of this technology into improved patient care, is essential to move the needle toward prevention and early detection and ultimately, to saving more lives from cancer.

THE AACR CALL TO ACTION

Late last year, as the FY 2016 appropriations bill was being finalized, a bipartisan majority of members of Congress called for a significant funding increase for the NIH. The result was a $2 billion budget increase for the NIH in FY 2016, the agency's first significant annual funding boost in more than a decade.

During Senate debate on this year's (FY 2017) appropriations bill that provides funding to the NIH, Senator Roy Blunt (R-MO), Chairman of the Senate Appropriations Subcommittee on Labor, Health and Human Services, Education, and Related Agencies, stated, "Last year, I made clear that sustained funding was as important as the increased investment. A pattern begins in the second year, and we have seized the opportunity this year to begin a pattern of increases for the NIH." Chairman Blunt backed up his words by proposing another $2 billion funding increase for the NIH in FY 2017.

The AACR is supportive of Senator Blunt's statement and action in his role as Subcommittee Chairman, especially because of the unprecedented scientific opportunities that exist today to improve the way we prevent, detect, diagnose, and treat cancer. Robust, sustained, and predictable investments in biomedical research, coupled with comparable funding increases for the FDA, will accelerate progress against cancer at this critical time in the cancer field.

The AACR also applauds Vice President Joe Biden's comprehensive proposal for preventing cancer and accelerating the discovery of new cancer treatments through the National Cancer Moonshot Initiative. This timely initiative has galvanized the cancer community and sparked a renewed dialogue on how we can speed the pace of progress for the benefit of all patients with cancer. Working together, we can capitalize on this unique moment in cancer research to harness the extraordinary knowledge obtained through past federal investments, and allow for the translation of this information into strategies to prevent, detect, diagnose, and treat cancer.

Therefore, the AACR respectfully urges Congress and the Administration to:

- **Support the Senate Appropriations Labor, Health and Human Services, Education, and Related Agencies Subcommittee's FY 2017 bill**, which proposes to provide an increase of $2 billion for the NIH in FY 2017.
- **Finalize a Senate version of the House-passed 21st Century Cures Act that includes crucial funding for the NIH to support the National Cancer Moonshot Initiative and other important strategic research initiatives.**
- **Support an FDA budget in FY 2017 of $2.85 billion, $120 million above its FY 2016 level**, to ensure support for regulatory science and the timely approval of therapeutics that are safe and effective.
- **Readjust the discretionary budget caps for FY 2018 and beyond**, which would allow our nation's policymakers to continue to provide robust, sustained, and predictable funding increases for the NIH, NCI, and FDA in future years.

By taking such actions, we will improve our nation's health, sustain our leadership in cancer research and biomedical science, and spur our innovation-based economy.

REFERENCES

1. Arteaga CL, Adamson PC, Engelman JA, Foti M, Gaynor RB, Hilsenbeck SG, et al. AACR Cancer Progress Report 2014. Clin Cancer Res 2014;20: S1–S112.

2. Ryerson AB, Eheman CR, Altekruse SF, Ward JW, Jemal A, Sherman RL, et al. Annual Report to the Nation on the Status of Cancer, 1975-2012, featuring the increasing incidence of liver cancer. Cancer 2016;122:1312–37.

3. American Cancer Society. Cancer Facts & Figures 2016. Atlanta, GA: American Cancer Society; 2016.

4. Cancer survivorship—United States, 1971-2001. MMWR Morb Mortal Wkly Rep 2004;53:526–9.

5. Howlader N, Noone AM, Krapcho M, Miller D, Bishop K, Altekruse SF, et al. SEER Cancer Statistics Review, 1975-2013, National Cancer Institute. Bethesda, MD. Available from: http://seer.cancer.gov/csr/1975_2013/, based on November 2015 SEER data submission, posted to the SEER website, April 2016 [accessed July 31, 2016].

6. World Health Organization. Global Status Report on Noncommunicable Diseases 2014. Geneva, Switzerland: World Health Organization; 2014.

7. Harding MC, Sloan CD, Merrill RM, Harding TM, Thacker BJ, Thacker EL. Abstract MP67: Transition from cardiovascular disease to cancer as the leading cause of death in US States, 1999-2013. Circulation 2016;133:AMP67–AMP.

8. Ferlay J, Soerjomataram I, Ervik M, Dikshit R, Eser S, Mathers C, et al. GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11 [Internet]. Lyon, France: International Agency for Research on Cancer; 2013. [cited 2016 July 31] Available from: http://globocan.iarc.fr.

9. Surveillance, Epidemiology, and End Results (SEER) Stat Fact Sheets: All Cancer Sites. National Cancer Institute 2016. [cited 2016 Jul 31] Available from: http://www.seer.cancer.gov/statfacts/html/all.html.

10. American Cancer Society. Cancer Facts & Figures for Hispanics/Latinos 2012-2014. Atlanta: American Cancer Society; 2012.

11. Siegel RL, Sahar L, Robbins A, Jemal A. Where can colorectal cancer screening interventions have the most impact? Cancer Epidemiol Biomarkers Prev 2015; 24:1151–6.

12. Bristow RE, Chang J, Ziogas A, Campos B, Chavez LR, Anton-Culver H. Sociodemographic disparities in advanced ovarian cancer survival and adherence to treatment guidelines. Obstet Gynecol 2015;125: 833–42.

13. Dilley JA, Simmons KW, Boysun MJ, Pizacani BA, Stark MJ. Demonstrating the importance and feasibility of including sexual orientation in public health surveys: health disparities in the Pacific Northwest. Am J Public Health 2010;100:460–7.

14. Buchmueller T, Carpenter CS. Disparities in health insurance coverage, access, and outcomes for individuals in same-sex versus different-sex relationships, 2000–2007. American J Public Health 2010;100:489–95.

15. U.S. Census Bureau International Programs. World Population by Age and Sex. [cited 2016 July 31; Available from: http://www.census.gov/population/international/data/worldpop/tool_population.php.

16. Centers for Disease Control and Prevention National Center for Health Statistics. Cancer. [cited; Available from: http://www.cdc.gov/nchs/fastats/cancer.htm.

17. Chowdhury PP, Mawokomatanda T, Xu F, Gamble S, Flegel D, Pierannunzi C, et al. Surveillance for certain health behaviors, chronic diseases, and conditions, access to health care, and use of preventive health services among states and selected local areas—behavioral risk factor surveillance system, United States, 2012. MMWR Surveill Summ 2016;65:1–142.

18. American Cancer Society. Cancer facts and figures 2014. Atlanta, GA: American Cancer Society; 2014.

19. Colby SL, Ortman JM. Projections of the Size and Composition of the U.S. Population: 2014 to 2060. Current Population Reports, P25-1143, U.S. Census Bureau, Washington, DC, 2014.

20. Ward BM, Clarke TC, Nugent CN, Schiller JS. Early Release of Selected Estimates Based on Data From the 2015 National Health Interview Survey. Centers for Disease Control and Prevention Available from: http://www.cdc.gov/nchs/data/nhis/earlyrelease/earlyrelease201605.pdf; 2016.

21. Bloom DE, Cafiero ET, Jané-Llopis E, Abrahams-Gessel S, Bloom LR, Fathima S, et al. The Global Economic Burden of Non-communicable Diseases. Geneva: World Economic Forum; 2011.

22. National Institutes of Health. The Genetics of Cancer. 2015 [cited 2016 July 31; Available from: http://www.cancer.gov/about-cancer/causes-prevention/genetics.

23. Tomasetti C, Vogelstein B. Variation in cancer risk among tissues can be explained by the number of stem cell divisions. Science 2015;347:78–81.

24. Baselga J, Bhardwaj N, Cantley LC, DeMatteo R, DuBois RN, Foti M, et al. AACR Cancer Progress Report 2015. Clin Cancer Res 2015;21:S1–128.

25. National Research Council (U.S.). Committee on a Framework for Developing a New Taxonomy of Disease. Toward precision medicine: Building a knowledge network for biomedical research and a new taxonomy of disease. Washington, D.C.: National Academies Press; 2011.

26. Rebbeck TR. Precision prevention of cancer. Cancer Epidemiol Biomarkers Prev 2014;23:2713–5.

27. Colditz GA, Wolin KY, Gehlert S. Applying what we know to accelerate cancer prevention. Sci Transl Med 2012;4:127rv4.

28. Sawyers CL, Abate-Shen C, Anderson KC, Barker A, Baselga J, et al. AACR Cancer Progress Report 2013. Clin Cancer Res 2013;19:S4–98.

29. Song M, Giovannucci E. Preventable incidence and mortality of carcinoma associated with lifestyle factors among white adults in the United States. JAMA Oncology 2016. 2016 May 19 [Epub ahead of print].

30. Stewart B, Wild CP, eds. World Cancer Report 2014. Lyon, France: International Agency for Research on Cancer.

31. Moolgavkar SH, Holford TR, Levy DT, Kong CY, Foy M, Clarke L, et al. Impact of reduced tobacco smoking on lung cancer mortality in the United States during 1975-2000. J Natl Cancer Inst 2012;104:541–8.

32. Pham N, Mandel N, Morales AC. Messages from the food police: how food-related warnings backfire among dieters. J Assoc Cons Res 2016;1:175–90.

33. Secretan B, Straif K, Baan R, Grosse Y, El Ghissassi F, Bouvard V, et al. A review of human carcinogens—Part E: tobacco, areca nut, alcohol, coal smoke, and salted fish. Lancet Oncol 2009;10:1033–4.

34. U.S. Department of Health and Human Services. The Health Consequences of Smoking—50 Years of Progress: A Report of the Surgeon General. Atlanta, GA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health; 2014.

35. Centers for Disease Control and Prevention Office on Smoking and Health. Fact Sheet on Smoking and Cancer. Atlanta (GA): Centers for Disease Control and Prevention; 2014. Available from http://www.cdc.gov/tobacco/data_statistics/sgr/50th-anniversary/pdfs/fs_smoking_cancer_508.pdf.

36. Lindson-Hawley N, Banting M, West R, Michie S, Shinkins B, Aveyard P. Gradual versus abrupt smoking cessation: a randomized, controlled noninferiority trial. Ann Intern Med 2016;164:585–92.

37. Bayne-Jones S, Burdette WJ, Cochran WG, Farber E, Fieser LF, Furth J, et al. Smoking and Health: A Report of the Advisory Commitee to the Surgeon General of the Public Health Service. Washington, D.C.: U.S. Department of Health, Education and Welfare, Public Health Service; 1964. Available from: http://profiles.nlm.nih.gov/ps/access/NNBBMQ.pdf.

38. Singh T, Arrazola RA, Corey CG, Husten CG, Neff LJ, Homa DM, et al. Tobacco use among middle and high school students—United States, 2011-2015. MMWR Morb Mortal Wkly Rep 2016;65:361-7.

REFERENCES

39. Holford TR, Meza R, Warner KE, Meernik C, Jeon J, Moolgavkar SH, et al. Tobacco control and the reduction in smoking-related premature deaths in the United States, 1964-2012. JAMA 2014;311:164–71.

40. Jamal A, Homa DM, O'Connor E, Babb SD, Caraballo RS, Singh T, et al. Current cigarette smoking among adults—United States, 2005-2014. MMWR Morb Mortal Wkly Rep 2015;64:1233–40.

41. Substance Abuse and Mental Health Services Administration. Results from the 2013 National Survey on Drug Use and Health: Summary of National Findings. Rockville (MD): Substance Abuse and Mental Health Services Administration; 2014.

42. Primack BA, Carroll MV, Weiss PM, Shihadeh AL, Shensa A, Farley ST, et al. Systematic review and meta-analysis of inhaled toxicants from waterpipe and cigarette smoking. Public Health Rep 2016;131:76–85.

43. Cobb C, Ward KD, Maziak W, Shihadeh AL, Eissenberg T. Waterpipe tobacco smoking: an emerging health crisis in the United States. Am J Health Behav 2010;34:275–85.

44. Brandon TH, Goniewicz ML, Hanna NH, Hatsukami DK, Herbst RS, Hobin JA, et al. Electronic nicotine delivery systems: a policy statement from the American Association for Cancer Research and the American Society of Clinical Oncology. Clin Cancer Res 2015;21:514–25.

45. Governing.com. State Marijuana Laws Map [cited 2016 July 31; Available from: http://www.governing.com/gov-data/state-marijuana-laws-map-medical-recreational.html.

46. Singh T, Marynak K, Arrazola RA, Cox S, Rolle IV, King BA. Vital Signs: Exposure to Electronic Cigarette Advertising Among Middle School and High School Students—United States, 2014. MMWR Morb Mortal Wkly Rep 2016;64:1403–8.

47. Morain SR, Winickoff JP, Mello MM. Have tobacco 21 laws come of age? N Engl J Med 2016;374:1601–4.

48. Medicine Io. Public Health Implications of Raising the Minimum Age of Legal Access to Tobacco Products. Washington, DC: The National Academies Press; 2015.

49. Cancer preventability estimates for diet, nutrition, body fatness, and physical activity. [cited; Available from: World Cancer Research Fund International: http://www.wcrf.org/int/cancer-facts-figures/preventability-estimates/cancer-preventability-estimates-diet-nutrition.

50. World Cancer Research Fund International. Cancer Prevention & Survival: summary of global evidence on diet, weight, physical activity & what increases or decreases your risk of cancer. Available from: http://www.wcrf.org/int/research-we-fund/continuous-update-project-findings-reports/summary-global-evidence-cancer; 2016.

51. Arnold M, Pandeya N, Byrnes G, Renehan AG, Stevens GA, Ezzati M, et al. Global burden of cancer attributable to high body-mass index in 2012: a population-based study. Lancet Oncol 2015;16:36–46.

52. Centers for Disease Control and Prevention. Fast Stats: Obesity and Overweight. 2016 [cited 2016 July 31; Available from: http://www.cdc.gov/nchs/fastats/obesity-overweight.htm.

53. Kann L, McManus T, Harris WA, Shanklin S, Flint KH, Hawkins J, et al. Youth risk behavior surveillance—United States, 2015. MMWR Surveill Summ 2016;65:1–174.

54. Ding D, Lawson KD, Kolbe-Alexander TL, Finkelstein EA, Katzmarzyk PT, van Mechelen W, et al. The economic burden of physical inactivity: a global analysis of major non-communicable diseases. Lancet 2016. 2016 July 27 [Epub ahead of print].

55. World Health Organization. Facts and figures on childhood obesity. 2014 [cited 2016 July 31; Available from: http://www.who.int/end-childhood-obesity/facts/en/.

56. Moore SC, Lee I, Weiderpass E, et al. Association of leisure-time physical activity with risk of 26 types of cancer in 1.44 million adults. JAMA Internal Medicine 2016;176:816–25.

57. U.S. Department of Health and Human Services: Step It Up! The Surgeon General's Call to Action to Promote Walking and Walkable Communities; 2015.

58. National Physical Activity Plan Alliance. Columbia SC: National Physical Activity Plan; 2016; 2016.

59. U.S. Department of Health and Human Services and U.S. Department of Agriculture. 2015–2020 Dietary Guidelines for Americans. Washington D.C.; Available at http://health.gov/dietaryguidelines/2015/guidelines/; 2015.

60. U.S. Department of Health and Human Services and Food and Drug Administration. Food Labeling: Revision of the Nutrition and Supplement Facts Labels. Federal Register;81:33741–999.

61. Moore LV, Thompson FE. Adults meeting fruit and vegetable intake recommendations—United States, 2013. MMWR Morb Mortal Wkly Rep 2015;64:709–13.

62. Kantor ED, Udumyan R, Signorello LB, Giovannucci EL, Montgomery S, Fall K. Adolescent body mass index and erythrocyte sedimentation rate in relation to colorectal cancer risk. Gut 2015;65:1289–95.

63. Zhang X, Wu K, Giovannucci EL, Ma J, Colditz GA, Fuchs CS, et al. Early life body fatness and risk of colorectal cancer in U.S. women and men—results from two large cohort studies. Cancer Epidemiol Biomarkers Prev 2015;24:690–7.

64. Farvid MS, Chen WY, Michels KB, Cho E, Willett WC, Eliassen AH. Fruit and vegetable consumption in adolescence and early adulthood and risk of breast cancer: population based cohort study. BMJ 2016;353:i2343.

65. U.S. Department of Health and Human Services. The Surgeon General's Call to Action to Prevent Skin Cancer. Washington D.C.: U.S. Department of Health and Human Services, Office of the Surgeon General; 2014.; 2014.

66. Wehner MR, Chren MM, Nameth D, Choudhry A, Gaskins M, Nead KT, et al. International prevalence of indoor tanning: a systematic review and meta-analysis. JAMA Dermatol 2014;150:390–400.

67. Holman DM, Berkowitz Z, Guy GP, Jr, Hawkins NA, Saraiya M, Watson M. Patterns of sunscreen use on the face and other exposed skin among US adults. J Am Acad Dermatol 2015;73:83–92.

68. Holman DM, Berkowitz Z, Guy GP, Jr, Hartman AM, Perna FM. The association between demographic and behavioral characteristics and sunburn among U.S. adults—National Health Interview Survey, 2010. Prev Med 2014;63:6–12.

69. Centers for Disease Control and Prevention. Use of indoor tanning devices by adults—United States, 2010. MMWR Morb Mortal Wkly Rep 2012;61:323–6.

70. Kann L, Kinchen S, Shanklin SL, Flint KH, Kawkins J, Harris WA, et al. Youth risk behavior surveillance—United States, 2013. MMWR Surveill Summ 2014;(63 Suppl 4):1–168.

71. Guy GP, Jr, Thomas CC, Thompson T, Watson M, Massetti GM, Richardson LC. Vital signs: melanoma incidence and mortality trends and projections—United States, 1982-2030. MMWR Morb Mortal Wkly Rep 2015;64:591–6.

72. Guy GP, Jr, Berkowitz Z, Jones SE, Olsen EO, Miyamoto JN, Michael SL, et al. State indoor tanning laws and adolescent indoor tanning. Am J Public Health 2014;104:e69–74.

73. Boniol M, Autier P, Boyle P, Gandini S. Cutaneous melanoma attributable to sunbed use: systematic review and meta-analysis. BMJ 2012;345:e4757.

74. Bouvard V, Baan R, Straif K, Grosse Y, Secretan B, El Ghissassi F, et al. A review of human carcinogens—Part B: Biological agents. Lancet Oncol 2009;10:321–2.

75. Chang Y, Moore PS. Merkel cell carcinoma: a virus-induced human cancer. Annu Rev Pathol 2012;7:123–44.

76. de Martel C, Ferlay J, Franceschi S, Vignat J, Bray F, Forman D, et al. Global burden of cancers attributable to infections in 2008: a review and synthetic analysis. Lancet Oncol 2012;13:607–15.

77. Viens LJ, Henley SJ, Watson M, Markowitz LE, Thomas CC, Thompson TD, et al. Human papillomavirus-associated cancers—United States, 2008-2012. MMWR Morb Mortal Wkly Rep 2016;65:661–6.

78. Centers for Disease Control and Prevention. Human papillomavirus-associated cancers—United States, 2004-2008. MMWR Morb Mortal Wkly Rep 2012;61:258–61.

REFERENCES

79. Roberts H, Kruszon-Moran D, Ly KN, Hughes E, Iqbal K, Jiles RB, et al. Prevalence of chronic hepatitis B virus (HBV) infection in U.S. households: National Health and Nutrition Examination Survey (NHANES), 1988-2012. Hepatology 2016;63:388–97.

80. Welzel TM, Graubard BI, Quraishi S, Zeuzem S, Davila JA, El-Serag HB, et al. Population-attributable fractions of risk factors for hepatocellular carcinoma in the United States. Am J Gastroenterol 2013;108:1314–21.

81. Accelerating HPV Vaccine Uptake: Urgency for Action to Prevent Cancer. A Report to the President of the United States from the President's Cancer Panel. Bethesda, MD: National Cancer Institute; 2014.

82. Reagan-Steiner S, Yankey D, Jeyarajah J, Elam-Evans LD, Singleton JA, Curtis CR, et al. National, regional, state, and selected local area vaccination coverage among adolescents aged 13-17 years—United States, 2014. MMWR Morb Mortal Wkly Rep 2015;64:784–92.

83. Binagwaho A, Wagner CM, Gatera M, Karema C, Nutt CT, Ngabo F. Achieving high coverage in Rwanda's national human papillomavirus vaccination programme. Bull World Health Organ 2012;90:623–8.

84. Raesima MM, Forhan SE, Voetsch AC, Hewitt S, Hariri S, Wang SA, et al. Human papillomavirus vaccination coverage among school girls in a demonstration project—Botswana, 2013. MMWR Morb Mortal Wkly Rep 2015;64:1147–9.

85. National Vaccine Advisory committee. Overcoming Barriers to Low HPV Vaccine Uptake in the United States: Recommendations from the National Vaccine Advisory Committee: Approved by the National Vaccine Advisory Committee on June 9, 2015. Public Health Rep 2016;131:17–25.

86. Gilkey MB, Malo TL, Shah PD, Hall ME, Brewer NT. Quality of physician communication about human papillomavirus vaccine: findings from a national survey. Cancer Epidemiol Biomarkers Prev 2015;24:1673–9.

87. Cantley LC, Dalton WS, DuBois RN, Finn OJ, Futreal PA, Golub TR, et al. AACR Cancer Progress Report 2012. Clin Cancer Res 2012;18:S1–100.

88. National Toxicology Program. Report on Carcinogens, 13th Edition. Research Triangle Park, NC: U.S. Department of Health and Human Services, Public Health Service; 2014. Available from: http://ntp.niehs.nih.gov/pubhealth/roc/roc13/index.html.

89. National Cancer Institute. Radon and Cancer. 2011 cited 2016 July 31; Available from: http://www.cancer.gov/about-cancer/causes-prevention/risk/substances/radon/radon-fact-sheet.

90. Loomis D, Grosse Y, Lauby-Secretan B, El Ghissassi F, Bouvard V, Benbrahim-Tallaa L, et al. The carcinogenicity of outdoor air pollution. Lancet Oncol 2013;14:1262–3.

91. Baris D, Waddell R, Beane Freeman LE, Schwenn M, Colt JS, Ayotte JD, et al. Elevated bladder cancer in Northern New England: the role of drinking water and arsenic. J Natl Cancer Inst 2016;108.

92. Blake JM, Avasarala S, Artyushkova K, Ali AM, Brearley AJ, Shuey C, et al. Elevated concentrations of U and co-occurring metals in abandoned mine wastes in a northeastern Arizona Native American community. Environ Sci Technol 2015;49:8506–14.

93. Kensler TW, Spira A, Garber JE, Szabo E, Lee JJ, Dong Z, et al. Transforming cancer prevention through precision medicine and immune-oncology. Cancer Prev Res (Phila) 2016;9:2–10.

94. Borras E, San Lucas FA, Chang K, Zhou R, Masand G, Fowler J, et al. Genomic landscape of colorectal mucosa and adenomas. Cancer Prev Res (Phila) 2016;9:417–27.

95. Levy AR, Bruen BK, Ku L. Health care reform and women's insurance coverage for breast and cervical cancer screening. Prev Chronic Dis 2012;9:E159.

96. Lindor NM, McMaster ML, Lindor CJ, Greene MH. Concise Handbook of Familial Cancer Susceptibility Syndromes—Second Edition. JNCI Monographs 2008;2008:3–93.

97. Spechler SJ. Barrett esophagus and risk of esophageal cancer: a clinical review. JAMA 2013;310:627–36.

98. Mattar MC, Lough D, Pishvaian MJ, Charabaty A. Current management of inflammatory bowel

disease and colorectal cancer. Gastrointest Cancer Res 2011;4:53–61.

99. Giovannucci E, Harlan DM, Archer MC, Bergenstal RM, Gapstur SM, Habel LA, et al. Diabetes and cancer: a consensus report. CA Cancer J Clin 2010;60:207–21.

100. Habib SL, Rojna M. Diabetes and risk of cancer. ISRN Oncol 2013;2013:583786.

101. Shaheen NJ, Falk GW, Iyer PG, Gerson LB. ACG Clinical Guideline: diagnosis and management of Barrett's esophagus. Am J Gastroenterol 2016;111:30–50; quiz 1.

102. Bibbins-Domingo K, Force USPST. Aspirin use for the primary prevention of cardiovascular disease and colorectal cancer: U.S. Preventive Services Task Force Recommendation Statement. Ann Intern Med 2016;164:836–45.

103. Louis DN, Perry A, Reifenberger G, von Deimling A, Figarella-Branger D, Cavenee WK, et al. The 2016 World Health Organization Classification of Tumors of the Central Nervous System: a summary. Acta Neuropathol 2016;131:803–20.

104. Louis DN, Ohgaki H, Wiestler OD, Cavenee WK, Burger PC, Jouvet A, et al. The 2007 WHO Classification of Tumours of the Central Nervous System. Acta Neuropathologica 2007;114:97–109.

105. Prowell TM, Theoret MR, Pazdur R. Seamless oncology-drug development. N Engl J Med 2016;374:2001–3.

106. Roberts KG, Li Y, Payne-Turner D, Harvey RC, Yang YL, Pei D, et al. Targetable kinase-activating lesions in Ph-like acute lymphoblastic leukemia. N Engl J Med 2014;371:1005–15.

107. Manyika J, Chui M, Brown B, Bughin J, Dobbs R, Roxburgh C, et al. Big data: The next frontier for innovation, competition, and productivity. New York, NY: McKinsey Global Institute; 2011.

108. Leslie Johnson. "Library of Congress" Worth of Data: It's All In How You Define It. 2012 [cited 2016 July 31]; Available from: http://blogs.loc.gov/digitalpreservation/2012/04/a-library-of-congress-worth-of-data-its-all-in-how-you-define-it/.

109. Bashor J. Weathering the Flood of Big Data in Climate Research 2014 [cited 2014 July 31]; Available from: http://www.es.net/news-and-publications/esnet-news/2014/weathering-the-flood-of-big-data-in-climate-research/.

110. Gantz J, Reinsel D. Extracting Value from Chaos. Framingham, MA: IDC IVIEW; 2011.

111. Lawrence MS, Stojanov P, Mermel CH, Robinson JT, Garraway LA, Golub TR, et al. Discovery and saturation analysis of cancer genes across 21 tumour types. Nature 2014;505:495–501.

112. Sehn LH, Chua N, Mayer J, Dueck G, Trněný M, Bouabdallah K, et al. Obinutuzumab plus bendamustine versus bendamustine monotherapy in patients with rituximab-refractory indolent non-Hodgkin lymphoma (GADOLIN): a randomised, controlled, open-label, multicentre, phase 3 trial. Lancet Oncol 2016;17:1081–93.

113. Centers for Disease Control and Prevention. Vital signs: colorectal cancer screening test use—United States, 2012. MMWR Morb Mortal Wkly Rep 2013;62:881–8.

114. Centers for Disease Control and Prevention. Vital signs: colorectal cancer screening, incidence, and mortality—United States, 2002-2010. MMWR Morb Mortal Wkly Rep 2011;60:884–9.

115. Centers for Disease Control and Prevention. CDC Vital Signs: Colorectal Cancer Tests Save Lives. Atlanta (GA): Centers for Disease Control and Prevention; 2013. Available from: http://www.cdc.gov/VitalSigns/pdf/2013-11-vitalsigns.pdf.

116. deVos T, Tetzner R, Model F, Weiss G, Schuster M, Distler J, et al. Circulating methylated SEPT9 DNA in plasma is a biomarker for colorectal cancer. Clin Chem 2009;55:1337–46.

117. News of Science. Science 1957;125:18–22.

118. National Academies of Science, Engineering, and Medicine. Appropriate use of advanced technologies for radiation therapy and surgery in oncology: Workshop summary. Washington DC: National Academies Press; 2016.

REFERENCES

119. Fleshman J, Sargent DJ, Green E, Anvari M, Stryker SJ, Beart RW, Jr, et al. Laparoscopic colectomy for cancer is not inferior to open surgery based on 5-year data from the COST Study Group trial. Ann Surg 2007;246:655–62; discussion 62–4.

120. Pearce SM, Pariser JJ, Karrison T, Patel SG, Eggener SE. Comparison of perioperative and early oncologic outcomes between open and robotic assisted laparoscopic prostatectomy in a contemporary population based cohort. J Urol;196:76–81.

121. Yaxley JW, Coughlin GD, Chambers SK, Occhipinti S, Samaratunga H, Zajdlewicz L, et al. Robot-assisted laparoscopic prostatectomy versus open radical retropubic prostatectomy: early outcomes from a randomised controlled phase 3 study. Lancet 2016. 2016 July 26 [Epub ahead of print].

122. Cooper MA, Ibrahim A, Lyu H, Makary MA. Underreporting of robotic surgery complications. J Healthc Qual 2015;37:133–8.

123. Doscher ME, Schreiber JE, Weichman KE, Garfein ES. Update on post-mastectomy lymphedema management. Breast J 2016. 2016 Jul 3 [Epub ahead of print].

124. Giuliano AE, Hunt K, Ballman KV, Beitsch PD, Whitworth PW, Blumencranz PW, et al. Ten-year survival results of ACOSOG Z0011: a randomized trial of axillary node dissection in women with clinical T1-2 N0 M0 breast cancer who have a positive sentinel node (Alliance). ASCO Meeting Abstracts 2016;34:1007.

125. Hofman MS, Lau WF, Hicks RJ. Somatostatin receptor imaging with 68Ga DOTATATE PET/CT: clinical utility, normal patterns, pearls, and pitfalls in interpretation. Radiographics 2015;35:500–16.

126. Nanni C, Schiavina R, Brunocilla E, Boschi S, Borghesi M, Zanoni L, et al. 18F-fluciclovine PET/CT for the detection of prostate cancer relapse: a comparison to 11C-choline PET/CT. Clin Nucl Med 2015;40:e386–91.

127. Haviland JS, Owen JR, Dewar JA, Agrawal RK, Barrett J, Barrett-Lee PJ, et al. The UK Standardisation of Breast Radiotherapy (START) trials of radiotherapy hypofractionation for treatment of early breast cancer: 10-year follow-up results of two randomised controlled trials. Lancet Oncol 2013;14:1086–94.

128. Whelan TJ, Pignol JP, Levine MN, Julian JA, MacKenzie R, Parpia S, et al. Long-term results of hypofractionated radiation therapy for breast cancer. N Engl J Med 2010;362:513–20.

129. Jagsi R, Griffith KA, Boike TP, Walker E, Nurushev T, Grills IS, et al. Differences in the acute toxic effects of breast radiotherapy by fractionation schedule: comparative analysis of physician-assessed and patient-reported outcomes in a large multicenter cohort. JAMA Oncol 2015;1:918–30.

130. Shaitelman SF, Schlembach PJ, Arzu I, Ballo M, Bloom ES, Buchholz D, et al. Acute and short-term toxic effects of conventionally fractionated vs hypofractionated whole-breast irradiation: a randomized clinical trial. JAMA Oncol 2015;1:931–41.

131. Bekelman JE, Sylwestrzak G, Barron J, Liu J, Epstein AJ, Freedman G, et al. Uptake and costs of hypofractionated vs conventional whole breast irradiation after breast conserving surgery in the United States, 2008-2013. JAMA 2014;312:2542–50.

132. Wang-Gillam A, Li CP, Bodoky G, Dean A, Shan YS, Jameson G, et al. Nanoliposomal irinotecan with fluorouracil and folinic acid in metastatic pancreatic cancer after previous gemcitabine-based therapy (NAPOLI-1): a global, randomised, open-label, phase 3 trial. Lancet 2016;387:545–57.

133. Demetri GD, von Mehren M, Jones RL, Hensley ML, Schuetze SM, Staddon A, et al. Efficacy and safety of trabectedin or dacarbazine for metastatic liposarcoma or leiomyosarcoma after failure of conventional chemotherapy: results of a phase III randomized multicenter clinical trial. J Clin Oncol 2016;34:786–93.

134. Schoffski P, Chawla S, Maki RG, Italiano A, Gelderblom H, Choy E, et al. Eribulin versus dacarbazine in previously treated patients with advanced liposarcoma or leiomyosarcoma: a randomised, open-label, multicentre, phase 3 trial. Lancet 2016;387:1629–37.

135. Mayer RJ, Van Cutsem E, Falcone A, Yoshino T, Garcia-Carbonero R, Mizunuma N, et al. Randomized

trial of TAS-102 for refractory metastatic colorectal cancer. N Engl J Med 2015;372:1909–19.

136. Riely GJ, Yu HA. EGFR: the paradigm of an oncogene-driven lung cancer. Clin Cancer Res 2015;21:2221–6.

137. Janne PA, Yang JC, Kim DW, Planchard D, Ohe Y, Ramalingam SS, et al. AZD9291 in EGFR inhibitor-resistant non–small-cell lung cancer. N Engl J Med 2015;372:1689–99.

138. Shaw AT, Gandhi L, Gadgeel S, Riely GJ, Cetnar J, West H, et al. Alectinib in ALK-positive, crizotinib-resistant, non–small-cell lung cancer: a single-group, multicentre, phase 2 trial. Lancet Oncol 2016;17: 234–42.

139. Shaw AT, Ou SH, Bang YJ, Camidge DR, Solomon BJ, Salgia R, et al. Crizotinib in ROS1-rearranged non–small-cell lung cancer. N Engl J Med 2014;371:1963–71.

140. Thatcher N, Hirsch FR, Luft AV, Szczesna A, Ciuleanu TE, Dediu M, et al. Necitumumab plus gemcitabine and cisplatin versus gemcitabine and cisplatin alone as first-line therapy in patients with stage IV squamous non-small cell lung cancer (SQUIRE): an open-label, randomised, controlled phase 3 trial. Lancet Oncol 2015;16:763–74.

141. Soria JC, Felip E, Cobo M, Lu S, Syrigos K, Lee KH, et al. Afatinib versus erlotinib as second-line treatment of patients with advanced squamous cell carcinoma of the lung (LUX-Lung 8): an open-label randomised controlled phase 3 trial. Lancet Oncol 2015;16:897–907.

142. Stilgenbauer S, Eichhorst B, Schetelig J, Coutre S, Seymour JF, Munir T, et al. Venetoclax in relapsed or refractory chronic lymphocytic leukaemia with 17p deletion: a multicentre, open-label, phase 2 study. Lancet Oncol 2016;17:768–78.

143. Moreau P, Masszi T, Grzasko N, Bahlis NJ, Hansson M, Pour L, et al. Oral ixazomib, lenalidomide, and dexamethasone for multiple myeloma. N Engl J Med 2016;374:1621–34.

144. Larkin J, Ascierto PA, Dreno B, Atkinson V, Liszkay G, Maio M, et al. Combined vemurafenib and cobimetinib in BRAF-mutated melanoma. N Engl J Med 2014;371:1867–76.

145. Chapman PB, Hauschild A, Robert C, Haanen JB, Ascierto P, Larkin J, et al. Improved survival with vemurafenib in melanoma with BRAF V600E mutation. N Engl J Med 2011;364:2507–16.

146. Hauschild A, Grob JJ, Demidov LV, Jouary T, Gutzmer R, Millward M, et al. Dabrafenib in BRAF-mutated metastatic melanoma: a multicentre, open-label, phase 3 randomised controlled trial. Lancet 2012;380:358–65.

147. Flaherty KT, Infante JR, Daud A, Gonzalez R, Kefford RF, Sosman J, et al. Combined BRAF and MEK inhibition in melanoma with BRAF V600 mutations. N Engl J Med 2012;367:1694–703.

148. Choueiri TK, Escudier B, Powles T, Mainwaring PN, Rini BI, Donskov F, et al. Cabozantinib versus everolimus in advanced renal-cell carcinoma. N Engl J Med 2015;373:1814–23.

149. Motzer RJ, Hutson TE, Glen H, Michaelson MD, Molina A, Eisen T, et al. Lenvatinib, everolimus, and the combination in patients with metastatic renal cell carcinoma: a randomised, phase 2, open-label, multicentre trial. Lancet Oncol 2015;16:1473–82.

150. Yao JC, Fazio N, Singh S, Buzzoni R, Carnaghi C, Wolin E, et al. Everolimus for the treatment of advanced, non-functional neuroendocrine tumours of the lung or gastrointestinal tract (RADIANT-4): a randomised, placebo-controlled, phase 3 study. Lancet 2016;387:968–77.

151. Yao JC, Hassan M, Phan A, Dagohoy C, Leary C, Mares JE, et al. One hundred years after "carcinoid": epidemiology of and prognostic factors for neuroendocrine tumors in 35,825 cases in the United States. J Clin Oncol 2008;26:3063–72.

152. Hodi FS, O'Day SJ, McDermott DF, Weber RW, Sosman JA, Haanen JB, et al. Improved survival with ipilimumab in patients with metastatic melanoma. N Engl J Med 2010;363:711–23.

153. Ribas A, Hamid O, Daud A, Hodi FS, Wolchok JD, Kefford R, et al. Association of pembrolizumab with tumor response and survival among patients with advanced melanoma. JAMA 2016;315:1600–9.

154. Brahmer J, Reckamp KL, Baas P, Crino L, Eberhardt WE, Poddubskaya E, et al. Nivolumab versus

docetaxel in advanced squamous-cell non–small-cell lung cancer. N Engl J Med 2015;373:123–35.

155. Borghaei H, Paz-Ares L, Horn L, Spigel DR, Steins M, Ready NE, et al. Nivolumab versus docetaxel in advanced nonsquamous non–small-cell lung cancer. N Engl J Med 2015;373:1627–39.

156. Garon EB, Rizvi NA, Hui R, Leighl N, Balmanoukian AS, Eder JP, et al. Pembrolizumab for the treatment of non–small-cell lung cancer. N Engl J Med 2015;372:2018–28.

157. Herbst RS, Baas P, Kim D-W, Felip E, Pérez-Gracia JL, Han J-Y, et al. Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non–small-cell lung cancer (KEYNOTE-010): a randomised controlled trial. Lancet 2016;387: 1540–50.

158. Motzer RJ, Escudier B, McDermott DF, George S, Hammers HJ, Srinivas S, et al. Nivolumab versus everolimus in advanced renal-cell carcinoma. N Engl J Med 2015;373:1803–13.

159. Ansell SM, Lesokhin AM, Borrello I, Halwani A, Scott EC, Gutierrez M, et al. PD-1 blockade with nivolumab in relapsed or refractory Hodgkin's lymphoma. N Engl J Med 2015;372:311–9.

160. Butte MJ, Keir ME, Phamduy TB, Sharpe AH, Freeman GJ. Programmed death-1 ligand 1 interacts specifically with the B7-1 costimulatory molecule to inhibit T cell responses. Immunity 2007;27:111–22.

161. Rosenberg JE, Hoffman-Censits J, Powles T, van der Heijden MS, Balar AV, Necchi A, et al. Atezolizumab in patients with locally advanced and metastatic urothelial carcinoma who have progressed following treatment with platinum-based chemotherapy: a single-arm, multicentre, phase 2 trial. Lancet 2016;387:1909–20.

162. Seiwert TY, Burtness B, Mehra R, Weiss J, Berger R, Eder JP, et al. Safety and clinical activity of pembrolizumab for treatment of recurrent or metastatic squamous cell carcinoma of the head and neck (KEYNOTE-012): an open-label, multicentre, phase 1b trial. Lancet Oncol 2016;17:956–65.

163. Gillison ML, Blumenschein G Jr, Fayette J, Guigay J, Colevas AD, Licitra L, et al. Nivolumab (nivo) vs investigator's choice (IC) for recurrent or metastatic (R/M) head and neck squamous cell carcinoma (HNSCC): CheckMate-141 [abstract]. In: Proceedings of the 107th Annual Meeting of the American Association for Cancer Research; 2016 Apr 16–20; New Orleans, LA Philadelphia (PA): AACR; Cancer Res 2016;76(14 Suppl):Abstract CT099 DOI:10.1158/1538-7445.AM2016-CT099.

164. Le DT, Uram JN, Wang H, Bartlett BR, Kemberling H, Eyring AD, et al. PD-1 Blockade in tumors with mismatch-repair deficiency. N Engl J Med 2015;372:2509–20.

165. Postow MA, Chesney J, Pavlick AC, Robert C, Grossmann K, McDermott D, et al. Nivolumab and ipilimumab versus ipilimumab in untreated melanoma. N Engl J Med 2015;372:2006–17.

166. Lokhorst HM, Plesner T, Laubach JP, Nahi H, Gimsing P, Hansson M, et al. Targeting CD38 with daratumumab monotherapy in multiple myeloma. N Engl J Med 2015;373:1207–19.

167. Lonial S, Dimopoulos M, Palumbo A, White D, Grosicki S, Spicka I, et al. Elotuzumab therapy for relapsed or refractory multiple myeloma. N Engl J Med 2015;373:621–31.

168. Andtbacka RH, Kaufman HL, Collichio F, Amatruda T, Senzer N, Chesney J, et al. Talimogene laherparepvec improves durable response rate in patients with advanced melanoma. J Clin Oncol 2015;33:2780–8.

169. American Cancer Society. Cancer Treatment and Survivorship Facts & Figures 2016-2017. Atlanta, GA: American Cancer Society; 2016.

170. Hudson MM, Ness KK, Gurney JG, Mulrooney DA, Chemaitilly W, Krull KR, et al. Clinical ascertainment of health outcomes among adults treated for childhood cancer. JAMA 2013;309:2371–81.

171. Friedman DL, Whitton J, Leisenring W, Mertens AC, Hammond S, Stovall M, et al. Subsequent neoplasms in 5-year survivors of childhood cancer: the Childhood Cancer Survivor Study. J Natl Cancer Inst 2010;102:1083–95.

172. Armstrong GT, Chen Y, Yasui Y, Leisenring W, Gibson TM, Mertens AC, et al. Reduction in late mortality

among 5-year survivors of childhood cancer. N Engl J Med 2016;374:833–42.

173. Piccart M, Rutgers E, van' t Veer L, Slaets L, Delaloge S, Viale G, et al. Primary analysis of the EORTC 10041/ BIG 3-04 MINDACT study: a prospective, randomized study evaluating the clinical utility of the 70-gene signature (MammaPrint) combined with common clinical-pathological criteria for selection of patients for adjuvant chemotherapy in breast cancer with 0 to 3 positive nodes [abstract]. In: Proceedings of the 107th Annual Meeting of the American Association for Cancer Research; 2016 Apr 16–20; New Orleans, LA Philadelphia (PA): AACR; Cancer Res 2016;76(14 Suppl):Abstract CT039 doi:101158/1538-7445AM2016-CT039.

174. Temel JS, Greer JA, Muzikansky A, Gallagher ER, Admane S, Jackson VA, et al. Early palliative care for patients with metastatic non-small cell lung cancer. N Engl J Med 2010;363:733–42.

175. Bakitas MA, Tosteson TD, Li Z, Lyons KD, Hull JG, Li Z, et al. Early versus delayed initiation of concurrent palliative oncology care: patient outcomes in the ENABLE III randomized controlled trial. J Clin Oncol 2015;33:1438–45.

176. El-Jawahri A, Jackson VA, Greer JA, Pirl WF, Park ER, Back A, et al. Early integrated palliative care to improve family caregivers (FC) outcomes for patients with gastrointestinal and lung cancer. ASCO Meeting Abstracts 2016;34:10131.

177. Davis MP, Temel JS, Balboni T, Glare P. A review of the trials which examine early integration of outpatient and home palliative care for patients with serious illnesses. Ann Palliat Med 2015;4:99–121.

178. Temel JS, El-Jawahri A, Greer JA, Pirl WF, Jackson VA, Park ER, et al. Randomized trial of early integrated palliative and oncology care. ASCO Meeting Abstracts 2016;34:10003.

179. El-Jawahri A, LeBlanc TW, Traeger L, VanDusen H, Jackson VA, Greer JA, et al. Randomized trial of an inpatient palliative care intervention in patients hospitalized for hematopoietic stem cell transplantation (HCT). ASCO Meeting Abstracts 2016;34:10004.

180. Institute of Medicine . Dying in America: Improving Quality and Honoring Individual Preferences Near the End of Life. Washington, DC: National Academies Press; 2015.

181. Cho J, Choi E, Kim I, Im Y, Park Y, Lee S, et al. Development and validation of chemotherapy-induced alopecia distress scale (CADS) for breast cancer patients. Ann Oncol 2014;25:346–51.

182. Ridderheim M, Bjurberg M, Gustavsson A. Scalp hypothermia to prevent chemotherapy-induced alopecia is effective and safe: a pilot study of a new digitized scalp-cooling system used in 74 patients. Support Care Cancer 2003;11:371–7.

183. Chien TJ, Liu CY, Chang YF, Fang CJ, Hsu CH. Acupuncture for treating aromatase inhibitor-related arthralgia in breast cancer: a systematic review and meta-analysis. J Altern Complement Med 2015;21:251–60.

184. Chakrabarty J, Vidyasagar M, Fernandes D, Joisa G, Varghese P, Mayya S. Effectiveness of pranayama on cancer-related fatigue in breast cancer patients undergoing radiation therapy: a randomized controlled trial. Int J Yoga 2015;8:47–53.

185. Dhruva A, Miaskowski C, Abrams D, Acree M, Cooper B, Goodman S, et al. Yoga breathing for cancer chemotherapy-associated symptoms and quality of life: results of a pilot randomized controlled trial. J Altern Complement Med 2012;18:473–9.

186. Bower JE, Garet D, Sternlieb B, Ganz PA, Irwin MR, Olmstead R, et al. Yoga for persistent fatigue in breast cancer survivors. Cancer 2012;118:3766–75.

187. Zick SM, Sen A, Wyatt GK, Murphy SL, Arnedt J, Harris RE. Investigation of 2 types of self-administered acupressure for persistent cancer-related fatigue in breast cancer survivors: a randomized clinical trial. JAMA Oncol 2016. 2016 Jul 7 [Epub ahead of print].

188. Nahin RL, Barnes PM, Stussman BJ. Expenditures on Complementary Health Approaches: United States, 2012. National Health Statistics Reports. Hyattsville, MD: National Center for Health Statistics. 2016.

189. Westmaas JL, Alcaraz KI, Berg CJ, Stein KD. Prevalence and correlates of smoking and cessation-

related behavior among survivors of ten cancers: findings from a nationwide survey nine years after diagnosis. Cancer Epidemiol Biomarkers Prev 2014;23:1783–92.

190. Toll BA, Brandon TH, Gritz ER, Warren GW, Herbst RS, AACR Subcommittee on Tobacco and Cancer, et al. Assessing tobacco use by cancer patients and facilitating cessation: an American Association for Cancer Research policy statement. Clin Cancer Res 2013;19:1941–8.

191. Land SR, Toll BA, Moinpour CM, Mitchell SA, Ostroff JS, Hatsukami DK, et al. Research priorities, measures, and recommendations for assessment of tobacco use in clinical cancer research. American Association for Cancer Research 2016;22:1907–13.

192. Betof AS, Dewhirst MW, Jones LW. Effects and potential mechanisms of exercise training on cancer progression: a translational perspective. Brain Behav Immun 2013;30 (Suppl):S75–87.

193. Brown JC, Schmitz KH. Weight lifting and physical function among survivors of breast cancer: a post hoc analysis of a randomized controlled trial. J Clin Oncol 2015;33:2184–9.

194. Winters-Stone KM, Laudermilk M, Woo K, Brown JC, Schmitz KH. Influence of weight training on skeletal health of breast cancer survivors with or at risk for breast cancer-related lymphedema. J Cancer Surviv 2014;8:260–8.

195. Biomedical Information Science and Technology Initiative Consortium. NIH Working Definition of Bioinformatics and Computational Biology. 2000 [cited 2014 July 31]; Available from: http://www.bisti.nih.gov/docs/compubiodef.pdf.

196. Wright AV, Nunez JK, Doudna JA. Biology and applications of CRISPR systems: harnessing nature's toolbox for genome engineering. Cell 2016;164:29–44.

197. Snyder A, Makarov V, Merghoub T, Yuan J, Zaretsky JM, Desrichard A, et al. Genetic basis for clinical response to CTLA-4 blockade in melanoma. N Engl J Med 2014;371:2189–99.

198. Van Allen EM, Miao D, Schilling B, Shukla SA, Blank C, Zimmer L, et al. Genomic correlates of response to CTLA-4 blockade in metastatic melanoma. Science 2015;350:207–11.

199. Sivan A, Corrales L, Hubert N, Williams JB, Aquino-Michaels K, Earley ZM, et al. Commensal bifidobacterium promotes antitumor immunity and facilitates anti-PD-L1 efficacy. Science 2015;350:1084–9.

200. Iida N, Dzutsev A, Stewart CA, Smith L, Bouladoux N, Weingarten RA, et al. Commensal bacteria control cancer response to therapy by modulating the tumor microenvironment. Science 2013;342:967–70.

201. Arpaia N, Campbell C, Fan X, Dikiy S, van der Veeken J, deRoos P, et al. Metabolites produced by commensal bacteria promote peripheral regulatory T-cell generation. Nature 2013;504:451–5.

202. Hirschey MD, DeBerardinis RJ, Diehl AM, Drew JE, Frezza C, Green MF, et al. Dysregulated metabolism contributes to oncogenesis. Semin Cancer Biol 2015;(35 Suppl):S129–50.

203. Boniol M, Autier P, Boyle P, Gandini S. Cutaneous melanoma attributable to sunbed use: systematic review and meta-analysis. BMJ 2012;345:e4757.

204. Lauby-Secretan B, Scoccianti C, Loomis D, Grosse Y, Bianchini F, Straif K. Body Fatness and Cancer—Viewpoint of the IARC Working Group. N Engl J Med 2016;375:794–8.

GLOSSARY

Acute lymphoblastic leukemia (ALL) An aggressive (fast-growing) type of leukemia (blood cancer) in which too many lymphoblasts (immature white blood cells) are found in the blood and bone marrow. Also called acute lymphocytic leukemia.

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 cancer (see **Non–small cell lung cancer**), some neuroblastomas (see **Neuroblastoma**), and some lymphomas—in particular, anaplastic large cell lymphomas.

Angiogenesis The process of growing new blood vessels from the existing vasculature. Angiogenesis is important for numerous normal body functions, as well as tumor growth and metastasis.

Basal cell carcinoma A form of skin cancer that begins in a type of cell in the skin that produces new skin cells as old ones die off. It is the most common cancer, but it rarely metastasizes (spreads to other parts of the body). Also called basal cell cancer.

B-cell lymphoma 2 (BCL-2) The BCL-2 gene makes the BCL-2 protein, which promotes cell survival by preventing cells from undergoing a natural self-destruct process called apoptosis. The BCL-2 gene is altered in many follicular lymphomas, and the BCL-2 protein has been implicated in some other forms of cancer, including chronic lymphocytic leukemia (see **Follicular lymphoma** and **Chronic lymphocytic leukemia**).

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.

Body mass index (BMI) Calculated as a person's weight in kilograms divided by height in meters. BMI provides an indicator of body fatness for most people, and it is often used to determine whether a person is underweight, of healthy weight, overweight, or obese.

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.

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.

Chronic lymphocytic leukemia (CLL) One of the most common types of leukemia (blood cancer) diagnosed

among adults in the United States. CLL arises in lymphocytes, most commonly B lymphocytes, in the bone marrow, which then enter the blood. It is usually slow growing, but in some people, it can be fast growing.

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

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

Colorectal cancer 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.

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.

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.

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.

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.

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.

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.

Familial adenomatous polyposis (FAP) An inherited condition in which numerous polyps (see **Polyp**) can develop in the colon and rectum. It increases the risk of colorectal cancer. Also called familial polyposis.

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

Follicular lymphoma A form of non-Hodgkin lymphoma that is usually slow growing. It begins in immune cells called B cells, which grow as groups to form nodules. It initially affects the lymph nodes and may spread to the bone marrow or spleen.

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.

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.

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.

Hurthle cell cancer A rare type of thyroid cancer (see **Thyroid cancer**).

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.

Janus kinase 2 (JAK2) The JAK2 gene makes the JAK2 protein, which is part of several signaling pathways that promote cell growth and proliferation (see **Signaling pathway/signaling network**). It is particularly important for controlling the production of blood cells.

Leukemia Cancer that starts in blood-forming tissue, such as the bone marrow, and causes large numbers of blood cells to be produced and enter the bloodstream.

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.

Mammalian target of rapomycin (mTOR) A protein that is part of several signaling pathways that regulate cell growth, cell proliferation, cell motility, cell survival, protein synthesis, and transcription. mTOR is also known as mechanistic target of rapamycin or FK506 binding protein 12-rapamycin-associated protein 1 (FRAP1).

Melanoma A form of cancer that begins in melanocytes (cells that make the pigment melanin). It may arise in a mole (skin melanoma), but it can also originate in other pigmented tissues, such as the eye (uveal melanoma) or the intestines (mucosal melanoma).

Metastasis The spread of cancer from one part of the body to another. A tumor formed by cells that have spread is called a metastatic tumor or a metastasis. The metastatic tumor contains cells that are like those in the original (primary) tumor. The plural form of metastasis is metastases.

Multiple myeloma A type of cancer that begins in plasma cells (white blood cells that produce antibodies). Also called Kahler disease, myelomatosis, and plasma cell myeloma.

GLOSSARY

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.

Nanotechnology Science, engineering, and technology conducted at the nanoscale, which is about 1 to 100 nanometers; for comparison, a sheet of paper is about 100,000 nanometers thick. Nanotechnology can be used in all other fields of science, such as chemistry, biology, physics, materials science, and engineering.

National Cancer Institute (NCI) The largest of the 27 research-focused institutes and centers of the National Institutes of Health. The NCI coordinates the National Cancer Program, which conducts and supports research, training, health information dissemination, and other programs with respect to the cause, diagnosis, prevention, and treatment of cancer; rehabilitation from cancer; and the continuing care of cancer patients and their families.

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

Noncommunicable diseases Diseases that are not passed from person to person, such as diabetes, cancer, and cardiovascular disease. Also called chronic disease.

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.

Oncolytic virus A virus that can preferentially infect and lyse (break down) cancer cells. Oncolytic viruses can occur naturally or can be made in the laboratory by changing other viruses.

Pancreatic cancer A group of cancers that start in cells of the pancreas, an organ located behind the stomach. Most pancreatic cancers begin in cells that make the digestive fluids, and the most common of these cancers are called adenocarcinomas. Cancers that arise in the pancreatic cells that help control blood sugar levels are called pancreatic neuroendocrine tumors (see **Neuroendocrine tumors**).

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.

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

Prevalence The number or percentage of people alive on a certain date in a population who previously had a diagnosis of a particular disease. It includes new and preexisting cases, and it is a function of both past incidence and survival.

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-1b** and **T cell**).

Proteasome A large protein complex found inside cells. It helps destroy other proteins when they are no longer needed.

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.

Renal cell carcinoma The most common form of kidney cancer diagnosed in U.S. adults. It begins in cells that line the tubules of the kidney, which is where blood is filtered and cleaned.

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

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

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.

T cell A type of immune cell that protects the body from invading microorganisms and other foreign substances and that destroys infected and malignant cells. A T cell is a type of white blood cell. Also called T lymphocyte.

Thyroid cancer Cancer that arises in the thyroid gland (a gland at the base of the neck that makes hormones that help control heart rate, blood pressure, body temperature, and weight). The four main types of thyroid cancer — papillary, follicular, medullary, and anaplastic — are named for the kind of cells found in the cancer and how the cancer cells look under a microscope.

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.

APPENDIX

SUPPLEMENTAL TABLE 1 FDA-APPROVED THERAPEUTICS FOR CANCER RISK REDUCTION OR TREATMENT OF PRECANCEROUS CONDITIONS*

Cancer Risk Reduction

Condition	Generic Name	Trade Name
Breast cancer	raloxifene	Evista
	tamoxifen	Nolvadex
Cervical, vulvar, vaginal, and anal cancers and dysplasia; genital warts	human papillomavirus quadrivalent vaccine (types 6, 11, 16, and 18)	Gardasil
Cervical, 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	Picato
	fluorouracil	Adricil
	diclofenac sodium	Voltaren
	5-aminolevulinic acid + photodynamic therapy (pdt)	
	masoprocol/ nordihydroguaiaretic acid	Actinex
Bladder dysplasia	bacillus calmette-guerin/BCG	
	valrubicin	Valstar
Esophageal dysplasia	porfimer sodium + photodynamic therapy (PDT)	Photofrin

*adapted from Wu X, Patterson S, Hawk E. Chemoprevention – History and general principles. Best Practice Research Clinical Gastroenterology. 2011;25:445-59.

SUPPLEMENTAL TABLE 2

FDA-APPROVED THERAPEUTICS FOR THE TREATMENT OF CANCER

DNA-synthesis Inhibitors (Antimetabolites)

Approved Indication	Generic Name	Trade Name
Multiple cancers	5-fluorouracil (5-FU)	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

INCREASING PRECISION ▼

Cell Cytoskeleton–modifying Agents

Approved Indication	Generic Name	Trade Name
Prostate cancer	cabazitaxel	Jevtana
Multiple cancers	docetaxel	Taxotere
Breast cancer; liposarcoma	eribulin mesylate	Halaven
Breast cancer	ixabepilone	Ixempra
Multiple cancers	paclitaxel	Taxol
Breast, lung, and pancreatic cancers	paclitaxel albumin-bound particles	Abraxane
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

Radiation-emitting Drugs

Approved Indication	Generic Name	Trade Name
Prostate cancer bone metastases	radium Ra 223 dichloride	Xofigo

SUPPLEMENTAL TABLE 2 *continued*

FDA-APPROVED THERAPEUTICS FOR THE TREATMENT OF CANCER

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	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

Proteasome Inhibitors

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

Protein-translation Inhibitors

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

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

INCREASING PRECISION ▼

DNA-repair Inhibitors

Approved Indication	Generic Name	Trade Name
Certain form of ovarian cancer*	olaparib	Lynparza

Immune-checkpoint Inhibitors

Approved Indication	Generic Name	Trade Name
Certain type of bladder cancer	atezolizumab	Tecentriq
Melanoma	ipilimumab	Yervoy
Multiple cancers	nivolumab	Opdivo
Melanoma; lung cancer*	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	regorafenib	Stivarga
Kidney cancer; certain type of thyroid cancer	sorafenib	Nexavar
Gastrointestinal stromal tumors; kidney cancer; some pancreatic cancers	sunitinib	Sutent
Thyroid cancer	vandetanib	Caprelsa
Colorectal cancer	ziv-aflibercept	Zaltrap

Cell-lysis Mediators

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

SUPPLEMENTAL TABLE 2 *continued*

FDA-APPROVED THERAPEUTICS FOR THE TREATMENT OF CANCER

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 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
Some leukemias	dasatinib	Sprycel
Certain type of melanoma*	dabrafenib	Tafinlar
Some lung cancers*; pancreatic cancer	erlotinib	Tarceva
Multiple cancers	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 form of lung cancer	necitumumab	Portrazza
Some leukemias	nilotinib	Tasigna
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
Myelofibrosis	ruxolitinib	Jakafi
Most common type of skin cancer	sonidegib	Odomzo
Certain types of melanoma*	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

INCREASING PRECISION ▼

* requires 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	Pancreatodudenectomy
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
Multiple cancers	Robotic or computer-assisted surgeries

Radiotherapy Treatments

Used to Treat	Procedure
Prostate, cervical, and 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, esophagus 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

INDEX

INDEX

O

P

R

S

T

U

V

W

X

Y

Z

615 Chestnut Street, 17th Floor, Philadelphia, PA 19106-4404

AACR American Association for Cancer Research

FINDING CURES TOGETHER℠

For your FREE copy of the full report, go to www.CancerProgressReport.org