AACR CANCER PROGRESS REPORT 2014

TRANSFORMING LIVES THROUGH RESEARCH

AACR American Association for Cancer Research

FINDING CURES TOGETHER℠

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A MESSAGE FROM THE AACR

Americans are more likely to survive a cancer diagnosis today than at any other time in history. In fact, thanks to the incredible strides that have been made in biomedical research, the percentage of the U.S. population living with, through, or beyond cancer has more than tripled since the U.S. Congress passed the National Cancer Act in 1971. The *AACR Cancer Progress Report 2014* chronicles the progress that has been made against the more than 200 diseases we call cancer and details how federal investment in the National Institutes of Health (NIH) and the National Cancer Institute (NCI) is transforming cancer care and the lives of patients in the United States and around the world.

Between Aug. 1, 2013, and July 31, 2014, the U.S. Food and Drug Administration (FDA) approved six new anticancer therapeutics and new uses for five previously approved anticancer therapeutics, two new cancer imaging agents, and one screening test. These advances add to the growing number of tools that health care providers have to detect, diagnose, treat, and cure some types of cancer. They are also helping patients like **James (Rocky) Lagno** (see p. 62), one of the individuals whose inspiring personal stories are included in the *AACR Cancer Progress Report 2014*, to live longer, fuller lives.

Rocky was diagnosed with lung cancer in 2011. When standard treatment with chemotherapy and radiation failed to stop the growth of his cancer, Rocky was advised by his physician to get his affairs in order; patients in his situation typically had about 13 months left to live. Rocky's tumor, however, tested positive for the ALK mutation that fuels 5 percent of non–small cell lung cancers (NSCLC). Armed with this information, Rocky's physicians prescribed him new treatments specifically designed for individuals with ALK-positive lung cancer, including ceritinib (Zykadia), a drug subsequently approved by the FDA in April 2014. Within weeks of receiving ceritinib, Rocky's condition improved dramatically, and he is currently experiencing a quality of life similar to what he had prior to his diagnosis.

Fortunately, Rocky's story is becoming more common. Paradigm-changing advances in biomedical research have made it possible to develop an increasing number of treatments precisely targeted to the unique molecular and genetic characteristics of an individual's cancer. In fact, five of the six anticancer therapeutics approved by the FDA between Aug. 1, 2013, and July 31, 2014, are compounds that actually target unique molecular and genetic characteristics.

Advances in cancer research have led to an expansion in the clinical use of genomic information, which was once reserved solely for research. Improvements in the ability to sequence and analyze large amounts of DNA have made it increasingly possible to identify the most appropriate therapy for a patient and to optimize the design and conduct of clinical trials. Collectively, these advances will spur the development of new and improved anticancer therapeutics.

The American Association for Cancer Research (AACR) is deeply grateful to all of the courageous individuals who have shared their personal experiences with the devastating collection of diseases we call cancer in the *AACR Cancer Progress Report 2014*. These stories, together with the advances described in this report, inspire hope for a future free of death from cancer. However, our ability to realize this future is in jeopardy because of reductions in federal investments in the NIH and NCI.

Budgets for the NIH and the NCI have failed to keep pace with inflation over the past decade. On top of these inflationary losses, direct budget cuts in 2011 and 2013 slashed NIH funding. With diminished resources, these critical agencies are not able to fund all of the promising research proposals they receive, and some researchers have had to downsize their laboratories or leave the field altogether. This reduction in our nation's research capacity and workforce has grave consequences for future innovation in biomedical research and, most importantly, for the more than 1.6 million people who are projected to receive a cancer diagnosis in the United States in 2014.

The AACR calls upon Congress and the administration to put the NIH and NCI budgets back on a path of predictable growth by providing annual budget increases

ARTEAGA FOTI

at least comparable to the biomedical inflation rate. In addition, policymakers must protect the NIH from future funding cuts by taking a balanced approach to long-term deficit reduction that prioritizes the federal investment in biomedical research. We urge all AACR members and, indeed, all Americans to join us in our quest to make cancer research a national priority. Cancer survivors like Rocky Lagno and the other individuals who shared their stories in this report, as well as those who are projected to receive a cancer diagnosis in the future, are depending on it.

Carlos L. Arteaga, MD
AACR President

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Chief Executive Officer

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ABOUT THE AMERICAN ASSOCIATION FOR CANCER RESEARCH

Founded in 1907, the American Association for Cancer Research (AACR) is the world's oldest and largest professional organization dedicated to advancing cancer research and its mission to prevent and cure cancer. AACR membership includes more than 35,000 laboratory, translational, and clinical researchers; population scientists; other health care professionals; and cancer advocates residing in 97 countries. The AACR marshals the full spectrum of expertise of the cancer community to accelerate progress in the prevention, biology, diagnosis, and treatment of cancer by annually convening more than 20 conferences and educational workshops, the largest of which is the AACR Annual Meeting with over 18,000 attendees. In addition, the AACR publishes eight 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 grants in cancer research that have the potential for near-term patient benefit. The AACR actively communicates with legislators and 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 has and will continue to fuel progress against cancer. This progress has been made possible by federal investment in biomedical research, which has expanded our knowledge of the biology of the more than 200 diseases we call cancer and allowed us to translate this knowledge into new and better ways to prevent, detect, diagnose, treat, and increasingly cure some of these diseases. Recent discoveries in the fields of cancer genomics and immunology have been particularly fruitful in this regard and hold great promise for the future.

An increased understanding of the role of genetic alterations in developing cancer is also the foundation on which changes are beginning to be made in the way that clinical trials are conducted and regulated. These changes can eliminate the need for large, long, multiphase trials, and it is hoped they will result in anticancer therapeutics receiving approval by the U.S. Food and Drug Administration (FDA) more rapidly than ever before.

Much of the research that has been particularly instrumental in building our current scientific foundation was funded by the federal government through the National Institutes of Health (NIH) and the National Cancer Institute (NCI).

The NIH:

comprises **27** institutes and centers;

annually funds **6,000** in-house scientists and 50,000 external grants at universities, medical schools, and research institutions;

and supports an estimated **432,000** jobs across the United States.

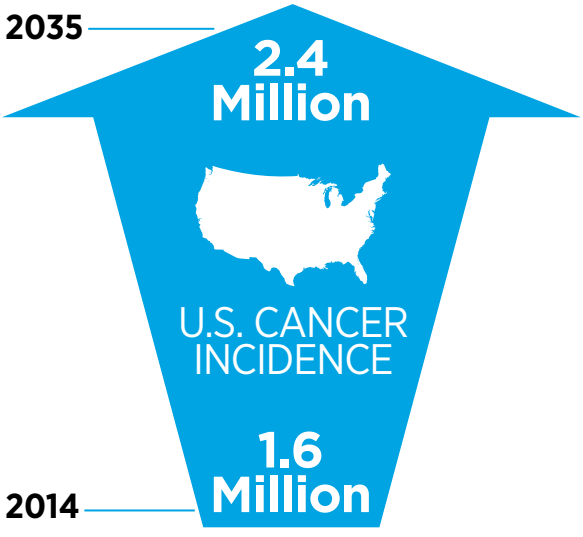
As the oldest and largest cancer organization in the world that fosters every aspect of high-quality, innovative cancer research, the American Association for Cancer Research (AACR) is committed to increasing public understanding of cancer and the importance of lifesaving cancer research, as well as advocating for increased federal research funding for the benefit of cancer survivors and their loved ones everywhere.

The fourth AACR Cancer Progress Report to Congress and the American public serves as a comprehensive educational tool that chronicles how research is transforming lives, such as the lives of the 12 courageous individuals who have shared their experiences with cancer within the report. The report also illustrates how unwavering bipartisan support from Congress and the administration, in the form of increased funding for the NIH and NCI, is required if we are to continue to transform lives through research in the future.

Cancer in 2014

Cancer research saves lives because it is the foundation of new and better strategies for cancer prevention, detection, diagnosis, and treatment. As a result, the number of people who are living longer, higher-quality lives after a cancer diagnosis continues to rise. In fact, it is estimated that in the United States alone, nearly 14.5 million cancer survivors are alive today; an estimated 379,112 of those individuals received their cancer diagnoses as children or adolescents.

Although extraordinary advances have been and continue to be made against cancer, it is estimated that 585,720 U.S. residents, including 1,960 children and adolescents, will die from some form of cancer in 2014. Moreover, because most cancer diagnoses occur in those age 65 and older, a segment of the U.S. population that is expected to double by 2060, we face a future in which the number of cancer-related deaths will increase dramatically unless new and better ways to prevent, detect, and treat cancer can be developed. These trends are being mirrored globally, and the number of people dying of cancer worldwide is expected to increase from 8.2 million in 2012 to 14.6 million in 2035.



As the number of cancer diagnoses increases, so, too, will the economic toll of the disease. Cancer is already among the most costly diseases to the United States. The most recent NIH estimates indicated that the overall economic costs of cancer to the United States in 2009 were $216.6 billion. When these costs are compared with the NIH and NCI budgets for fiscal year 2014, which are just $30 billion and $4.9 billion, respectively, it underscores the inadequacy in federal funding for cancer research that exists today.

Developing Cancer

Cancer arises when the orderly processes that control the multiplication and life span of normal cells go awry. The resultant changes in cell behavior are predominantly a result of alterations, or mutations, in the genetic material of the cells. The specific mutation, and the order and speed at which mutations accumulate, coupled with a person's genetic makeup and lifestyle factors such as tobacco use, diet, and physical activity, influence the rate at which cancer develops and progresses.

Although genetic mutations that lead to malfunctions in a cell underpin cancer initiation and development in most cases, interactions between cancer cells and their environment—known as the tumor microenvironment—as well as interactions with systemic factors, influence the development and progression of the disease. Thus, if we are to advance our mission to prevent and cure all cancers, we must develop a more comprehensive, whole-patient understanding of cancer.

The dedicated work of researchers throughout the biomedical research enterprise has expanded and continues to expand our knowledge of cancer. As our knowledge has grown so has our ability to exploit it to improve health care. Most of the new approaches to cancer treatment more precisely attack cancers than do traditional therapies, providing patients with not just longer but also higher-quality lives.

Healthy Living Can Prevent Cancer From Developing, Progressing, or Recurring

Many of the greatest reductions in the morbidity and mortality of cancer are a result of advances in cancer prevention that have come about as we have learned more about the factors that increase a person's risk of developing cancer.

Many factors that increase the risk of developing cancer are related to lifestyle, and it is estimated that more than 50 percent of the 585,720 cancer deaths expected to occur in the United States in 2014 will be related to preventable causes. Most notable among these causes 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. As a result, adopting a healthy approach to living that eliminates or reduces these risks, where possible, could significantly decrease the number of people diagnosed with certain types of cancer.

> *"Knowing what's right doesn't mean much unless you do what's right."*
>
> THEODORE ROOSEVELT

Importantly, healthy approaches to living can also reduce cancer recurrence and improve outcomes following a cancer diagnosis. However, a great deal more research and resources are needed to understand how best to help individuals change their lifestyle.

Cancer screening is another important part of a healthy lifestyle because finding a cancer early, before it has spread to other parts of the body, increases the likelihood that treatment can be curative. Given that each individual has unique risks for developing each type of cancer, everyone should consult with his or her physicians to develop a personalized cancer-screening plan that takes into account evidence-based recommendations; the individual's own

cancer risks, including family history; and the individual's tolerance of potential benefits and harms of screening.

Transforming Lives Through Research

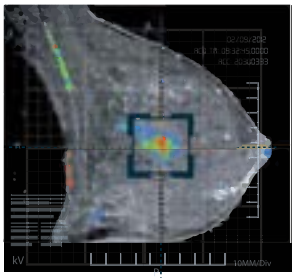
The dedicated efforts of individuals working throughout the cycle of biomedical research have led to extraordinary advances across the continuum of clinical care that are transforming lives in the United States and worldwide.

As a result of research advances, the FDA approved six new anticancer therapeutics in the 12 months leading up to July 31, 2014. During this time, the FDA also approved new uses for five previously approved anticancer therapeutics, a new use for a previously approved test for detecting the cancer-causing pathogen human papillomavirus (HPV), and new uses for two imaging agents.

FROM AUG. 1, 2013, TO JULY 31, 2014, THE FDA HAS APPROVED:

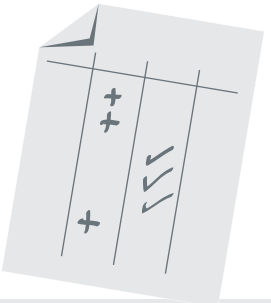
6 new anticancer therapeutics.

5 new uses for previously approved anticancer therapeutics.



2 new uses for imaging agents.

1 new use for a screening test.



Five of the new anticancer therapeutics approved by the FDA target specific molecules involved in the cancer process and are referred to as molecularly targeted therapeutics. They are part of a revolution in cancer treatment that began just over a decade ago. This revolution is changing the standard of cancer care from a one-size-fits-all approach to one in which the molecular makeup of the patient and his or her tumor dictates the best therapeutic strategy. This approach is often called personalized cancer medicine.

One of the new anticancer therapeutics approved by the FDA is also an immunotherapeutic. Cancer immunotherapy is a relatively new approach to cancer treatment that has begun to transform the lives of patients with certain cancers. There are several types of cancer immunotherapy, each of which works in a different way to train a patient's immune system to destroy the cancer. A number of cancer immunotherapeutics are showing immense promise in clinical trials, with some patients having remarkable and long-lasting responses.

As a result of research advances, more people than ever before are surviving longer and leading fuller lives after a cancer diagnosis. Despite this, cancer survivors often face serious and persistent adverse outcomes, including physical, emotional, psychosocial, and financial challenges as a result of their cancer diagnosis and treatment. 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. Individuals who receive a cancer diagnoses as children, adolescents, young adults, or when elderly, are particularly vulnerable to treatment-related health issues. Research is being performed to help all cancer survivors meet the numerous challenges they face.

~4%

of the U.S. population is a cancer survivor (3).

What Progress Does the Future Hold?

The genetic information about cancer initiation and development that we have learned through genomics research has been central to the personalized cancer medicine revolution. This new knowledge is now beginning to be used to reform how clinical trials are designed and conducted. As we look to the future, we can expect to see greater deployment of genomics and computational biology,

which will spur the development of many more anticancer therapeutics and new uses for our current treatment arsenal.

Great strides have been made toward improved cancer prevention, detection, diagnosis, treatment, and, in certain cases, cure. However, some groups of individuals—in particular, racial and ethnic minorities—experience notably higher incidence of some types of cancer than the general population and/or suffer significantly poorer treatment outcomes. As research increases our understanding of the many complex and interrelated causes of cancer health disparities, we will be able to develop and implement new interventions that will transform lives, regardless of race, ethnicity, age, gender, socioeconomic status, and place of residence.

"I am supremely confident that we will continue to make rapid progress in the future."

AACR PRESIDENT, 2014–2105,
CARLOS L. ARTEAGA, MD

A Prescription for Increasing the Rate of Progress Against Cancer

Federal support for the NIH and NCI has facilitated extraordinary progress against cancer. It has also catalyzed an explosion in our knowledge of the biology of cancer and understanding of how to apply this knowledge to provide new ways to reduce the burden of this disease. Despite these opportunities, many challenges must be overcome if we are to realize our goal of defeating cancer.

First and foremost, we must continue to pursue a comprehensive understanding of the biology of cancer at all stages and to develop new approaches to translating this knowledge into health care advances that will save lives. To do this, we must make investing in biomedical research a national priority. Only by investing in research talent, tools, and infrastructure and by advancing policies that drive innovation and the translation of new knowledge for the benefit of patients will we be able to capitalize on past federal investments in biomedical research and seize opportunities to forge ahead to the day when cancer is removed as a major health threat to all.

AACR CALL TO ACTION

We are now at a crossroads in our country's long struggle to prevent and cure cancer; we must choose between two paths, but there is only one viable path forward to continue transforming lives.

On the viable path we seize the momentum at this exciting time in biomedical research by committing to budget increases for the NIH and NCI so that the remarkable progress of the past can continue at a rapid pace.

To take the alternative path is simply unacceptable. This particularly dangerous path leads us to a place where federal funding for biomedical research remains stagnant or, even worse, declines, seriously jeopardizing the rate at which we are able to make progress. On this path, breakthroughs and discoveries will be slowed, meaning that delivery of the cures that patients and their loved ones desperately need is delayed. Early-career researchers may be forced to leave science for other fields, further jeopardizing continued future progress.

The AACR respectfully urges Congress to do the right thing for cancer patients and our nation and choose the only viable path forward, which is to:

Prioritize the growth of the NIH and NCI budgets at a predictable, robust pace by providing annual budget increases at least comparable to the biomedical inflation rate.

Rededicating our country to the promise of biomedical research requires strong leadership from the administration and Congress. It also requires a commitment from all Americans to support federal funding for biomedical research and to communicate this view to policymakers.

As a country we must set priorities and make difficult choices at this fiscally challenging time in our history. Our federal government can do no better than invest robustly in the NIH and the NCI so that the path forward will lead us to a brighter future for the millions of people whose lives have been touched by cancer.

A YEAR IN PROGRESS

2014

Today, **1 in 22 people** is a cancer survivor

14.5 MILLION SURVIVORS

379,112 of these individuals received their cancer diagnoses as children or adolescents.

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

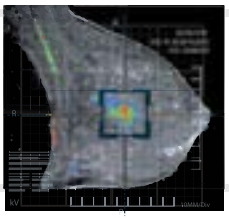
3 MILLION SURVIVORS

1971

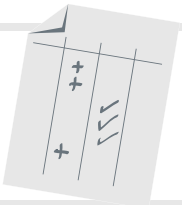
FROM AUG. 1, 2013, TO JULY 31, 2014, THE FDA HAS APPROVED:

6 new anticancer therapeutics.

5 new uses for previously approved anticancer therapeutics.



2 new uses for imaging agents.



1 new use for a screening test.

GENOMICS RESEARCH IS:

pinpointing new drug targets, p. 34.

identifying new patients for existing drugs, p. 40.

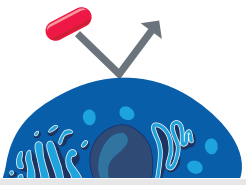
catalyzing novel clinical trial designs, p. 35.

RESEARCH IS TRANSFORMING LIVES BY ALLOWING US TO:

advance immunotherapeutic development, p. 64.

develop new molecularly targeted therapeutics, p. 52.

overcome drug resistance, p. 56.



CANCER IN 2014

IN THIS SECTION YOU WILL LEARN:

- THERE ARE NEARLY 14.5 MILLION CANCER SURVIVORS IN THE UNITED STATES.
- IN THE UNITED STATES, MORE THAN 1.6 MILLION PEOPLE ARE PROJECTED TO RECEIVE A CANCER DIAGNOSIS IN 2014, AND MORE THAN 585,000 ARE EXPECTED TO DIE FROM THE DISEASE.
- THE NUMBER OF NEW CANCER CASES PER YEAR IS PREDICTED TO RISE TO ALMOST 2.4 MILLION IN THE UNITED STATES, AND MORE THAN 24 MILLION GLOBALLY IN 2035.
- CANCER IS A COSTLY DISEASE, BOTH IN THE UNITED STATES AND WORLDWIDE.

Research Fuels Progress Against Cancer

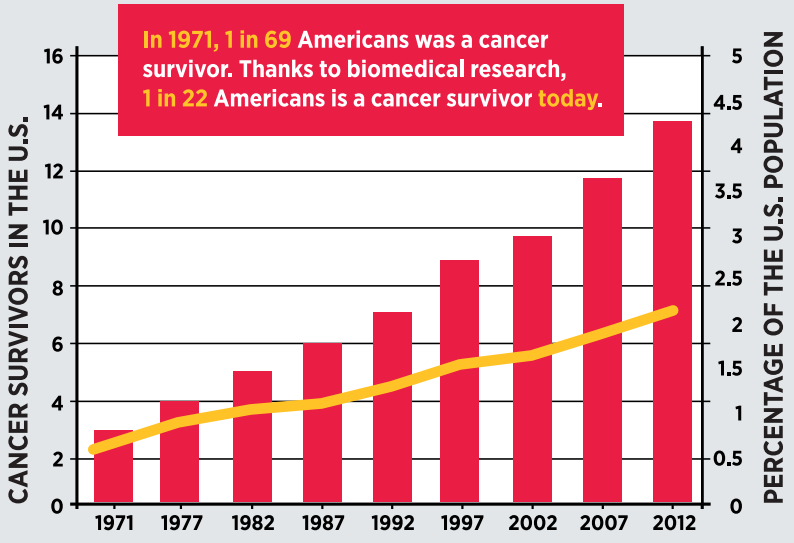
Research continues to be our best defense against cancer. It improves survival and quality of life for millions of individuals by spurring the development of new and better ways to prevent, detect, diagnose, treat, and, increasingly, cure some of the more than 200 diseases we call cancer.

This progress against cancer is the result of the dedicated efforts of many individuals working together as part of the broader biomedical research community (see sidebar on **The Biomedical Research Community**, p. 2). It takes many years of work by all stakeholders within this community to bring a new medical product from initial research discovery to approval by the U.S. Food and Drug Administration (FDA). This achievement was attained for six new anticancer therapeutics between Aug. 1, 2013, and July 31, 2014 (see **Table 1**, p. 3). During this period, the FDA also approved new uses for five previously approved anticancer therapeutics, two imaging agents, and one screening test, thereby increasing the number of patients benefiting from them.

As a result of advances like these, the number of people in the United States who survive their cancer continues to increase year after year (see **Figure 1**). In fact, since 1971, the year the U.S. Congress passed the National Cancer Act, the percentage of the U.S. population living with, through, or beyond a cancer diagnosis has more than tripled (1-4).

FIGURE 1 | **I WILL SURVIVE**

The number of cancer survivors in the United States has steadily increased since 1971 [red bars]. During the same period, the proportion of the nation's population that is living with, through, or beyond a cancer diagnosis has more than tripled [gold line]. Adapted from (5).



THE BIOMEDICAL RESEARCH COMMUNITY

By working together, the stakeholders in the biomedical research community have made and continue to make lifesaving progress against cancer for the benefit of patients, survivors, and their families. Among these stakeholders are the following:

patients, survivors, and their families and friends;

clinicians;

academic researchers from a wide range of specialties;

biotechnology, pharmaceutical, and diagnostics companies;

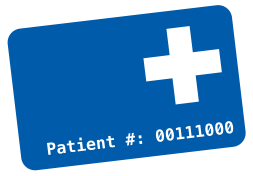
citizen advocates, and advocacy and philanthropic organizations;

policymakers;

regulatory agencies;

funding agencies; and

payers.



14.5 million

Americans with a history of cancer were estimated to be alive on Jan. 1, 2014 (3).

The basic, translational, and clinical research that has fueled and continues to fuel extraordinary progress against cancer is made possible by investments from the federal government, philanthropic individuals and organizations, and the private sector. Of particular importance are the investments in biomedical research supported by the federal government and administered through the National Institutes of Health (NIH) and the National Cancer Institute (NCI). Without sustained support of biomedical research from all sectors, continued progress against cancer is in jeopardy.

TABLE 1 | **NEWLY FDA-APPROVED THERAPEUTICS, AND INDICATIONS FOR THE TREATMENT AND IMAGING OF CANCER: AUGUST 1, 2013-JULY 31, 2014**

ANGIOGENESIS INHIBITORS

Approved Indication	Generic Name	Trade Name	Formulation
certain types of stomach cancer	ramucirumab	Cyramza	
certain type of thyroid cancer*	sorafenib	Nexavar	

BLOOD CANCER-SPECIFIC THERAPEUTIC ANTIBODY

Approved Indication	Generic Name	Trade Name	Formulation
certain type of leukemia	obinutuzumab†	Gazyva	

CELL CYTOSKELETON MODIFYING AGENTS

Approved Indication	Generic Name	Trade Name	Formulation
pancreatic cancer*	paclitaxel albumin-bound particles	Abraxane	

CELL SIGNALING INHIBITORS

Approved Indication	Generic Name	Trade Name	Formulation
certain type of melanoma	dabrafenib **and** trametinib^	Tafinlar **and** Mekinist	
certain types of leukemia and lymphoma	ibrutinib†	Imbruvica	
certain types of leukemia and lymphoma	idelalisib†	Zydelig	
HER2+ breast cancer*	pertuzumab	Perjeta	
certain type of metastatic ALK-positive lung cancer	ceritinib†	Zykadia	

EPIGENOME-MODIFYING AGENTS

Approved Indication	Generic Name	Trade Name	Formulation
certain type of non-Hodgkin lymphoma	belinostat	Beleodaq	

IMAGING AGENTS

Approved Indication/Use	Generic Name	Trade Name	Formulation
identification and staging of breast cancer*	gadobutrol	Gadavist	
certain type of head and neck cancer*	technetium 99m tilmanocept	Lymphoseek	

^ First approval of a combination of targeted therapies for the same indication

* New indication for 2013–2014

† Breakthrough therapy

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

Cancer: An Ongoing Challenge

Even though definitive, measurable progress has been and continues to be made against cancer, this devastating collection of diseases continues to pose an enormous challenge for researchers, clinicians, and patients. In fact, cancer remains the leading cause of disease-related death among children in the United States (1).

5-year survival rate
for all cancers (1)

1975–1977	2003–2009
49%	68%

TABLE 2 | ESTIMATED INCIDENCE AND MORTALITY FOR SELECT CANCERS

	Estimated 2014 Incidence*			Estimated 2014 Deaths*		
	Total	**Male**	**Female**	**Total**	**Male**	**Female**
ALL SITES	1,665,540	855,220	810,320	585,720	310,010	275,710
HEAD AND NECK REGION						
Brain & other nervous system	23,380	12,820	10,560	14,320	8,090	6,230
Oral cavity & pharynx	42,440	30,220	12,220	8,390	5,730	2,660
Tongue	13,590	9,720	3,870	2,150	1,450	700
Mouth	11,920	7,150	4,770	2,070	1,130	940
Pharynx	14,410	11,550	2,860	2,540	1,900	640
Larynx	12,630	10,000	2,630	3,610	2,870	740
Lung & bronchus	224,210	116,000	108,210	159,260	86,930	72,330
Breast	235,030	2,360	232,670	40,430	430	40,000
GASTROINTESTINAL (GI) SYSTEM						
Esophagus	18,170	14,660	3,510	15,450	12,450	3,000
Stomach	22,220	13,730	8,490	10,990	6,720	4,270
Liver & intrahepatic bile duct	33,190	24,600	8,590	23,000	15,870	7,130
Gallbladder & other biliary	10,650	4,960	5,690	3,630	1,610	2,020
Pancreas	46,420	23,530	22,890	39,590	20,170	19,420
Small intestine	9,160	4,880	4,280	1,210	640	570
Colon and Rectum†	96,830	48,450	48,380	50,310	26,270	24,040
UROGENITAL SYSTEM						
Kidney & renal pelvis	63,920	39,140	24,780	13,860	8,900	4,960
Ovary	21,980		21,980	14,270		14,270
Uterine corpus	52,630		52,630	8,590		8,590
Uterine cervix	12,360		12,360	4,020		4,020
Urinary bladder	74,690	56,390	18,300	15,580	11,170	4,410
Prostate	233,000	233,000		29,480	29,480	
Testis	8,820	8,820		380	380	
Skin (excluding basal & squamous)	81,220	46,630	34,590	12,980	8,840	4,140
Melanoma-skin	76,100	43,890	32,210	9,710	6,470	3,240
HEMATALOGICAL SYSTEM						
Leukemia	52,380	30,100	22,280	24,090	14,040	10,050
Acute lymphocytic leukemia	6,020	3,140	2,880	1,440	810	630
Chronic lymphocytic leukemia	15,720	9,100	6,620	4,600	2,800	1,800
Acute myeloid leukemia	18,860	11,530	7,330	10,460	6,010	4,450
Chronic myeloid leukemia	5,980	3,130	2,850	810	550	260
Lymphoma	79,990	43,340	36,650	20,170	11,140	9,030
Hodgkin lymphoma	9,190	5,070	4,120	1,180	670	510
Non-Hodgkin lymphoma	70,800	38,270	32,530	18,990	10,470	8,520
Myeloma	24,050	13,500	10,550	11,090	6,110	4,980
OTHER CANCERS						
Bones & joints	3,020	1,680	1,340	1,460	830	630
Soft tissue (including heart)	12,020	6,550	5,470	4,740	2,550	2,190

* Rounded to the nearest 10; estimated new cases exclude basal cell and squamous cell skin cancers and in situ carcinomas except urinary bladder. About 64,640 carcinoma in situ of the female breast and 61,300 melanoma in situ will be newly diagnosed in 2013.

† 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 1995-2009 as reported by the North American Association of Central Cancer Registries (NAACCR), represesnting about 98% of the US population. Estimated deaths are based on U.S. mortality data during 1995-2009, National Center for Health Statistics, Centers for Disease Control and Prevention.

Among the challenges we face is the fact that advances have not been uniform for all types of adult and pediatric cancer (see **Table 2**, p. 4 and **Table 3** , p. 6). Thus, whereas overall five-year survival rates for women with invasive breast cancer and men with prostate cancer are 89 percent and 99 percent, respectively, those for adult patients with pancreatic, liver, or lung cancer are very low, at 6 percent, 16 percent, and 17 percent, respectively (1). Similarly, whereas the overall five-year survival rate for childhood acute lymphoblastic leukemia (ALL) is 90 percent, it is only 64 percent for children diagnosed with rhabdomyosarcoma (1).

Moreover, advances have not been uniform for all patients diagnosed with a given cancer type. Five-year survival rates vary with stage at diagnosis and among different segments of the population (see sidebar on **Cancer Health Disparities in the United States**).

CANCER HEALTH DISPARITIES IN THE UNITED STATES

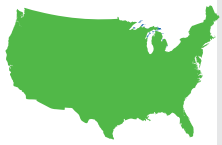
Cancer health disparities are defined as differences in cancer incidence, prevalence, treatment, and outcome among certain segments of a population, including:

racial and ethnic minority groups;

individuals with low socioeconomic status;

individuals who lack or have limited access to healthcare;

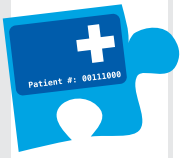
residents in certain geographical locations, including rural areas; and



the elderly.

Complex and interrelated factors contribute to disparities in cancer incidence and death among these medically underserved groups. These factors may include, but are not limited to, differences or inequities in:

access to and use of health care;



treatments received;

exposure to environmental cancer risk factors;

genetics;

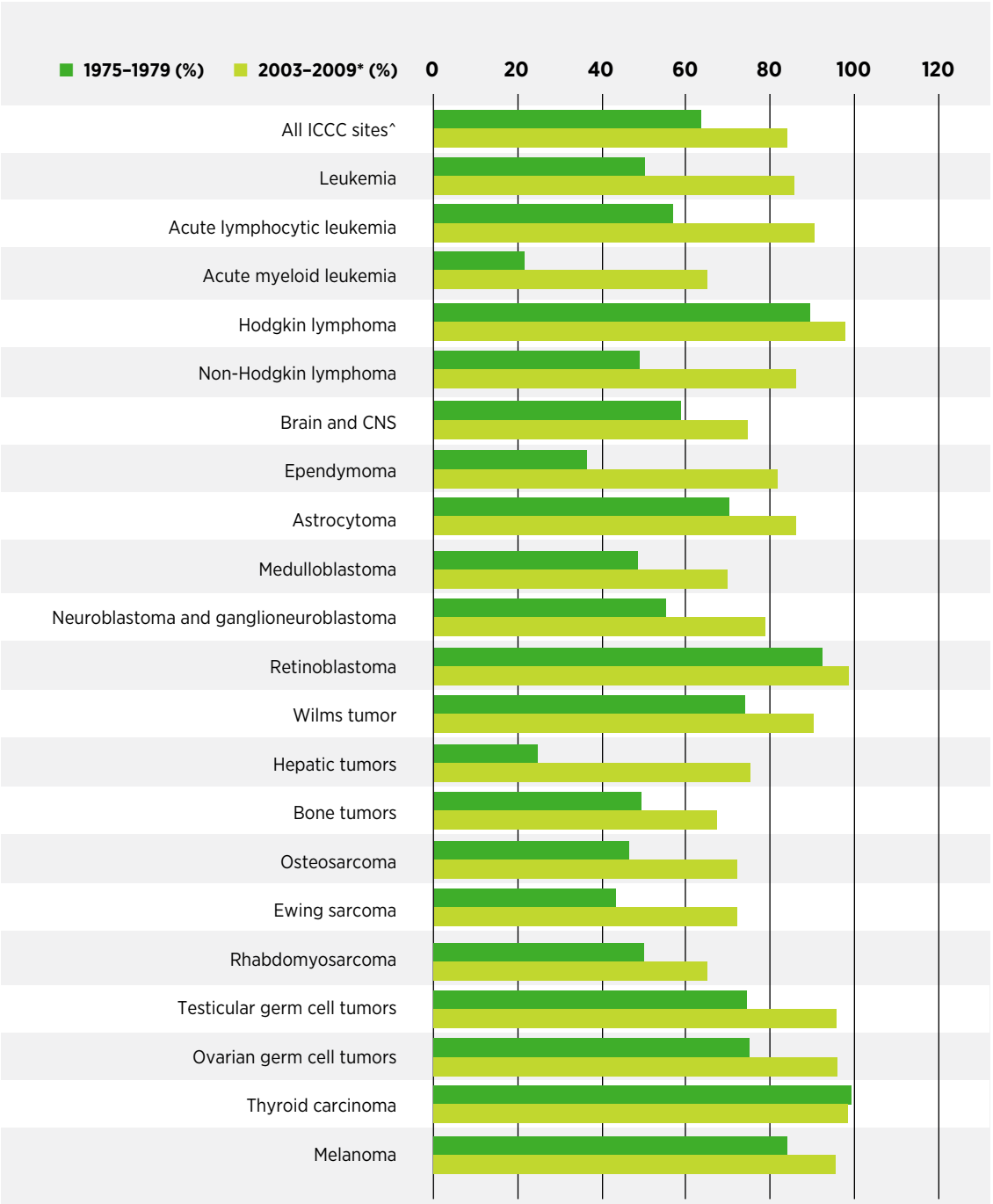
social and economic status;

cultural beliefs; and

health literacy.

The interdependent nature of many of these variables makes it difficult to isolate and study the relative contribution of each to cancer health disparities. However, given that a significant proportion of the U.S. population falls into one or more categories of people at risk of experiencing a disparity, it is important that research into these difficult issues continues. Only with new insights will we develop and implement innovative interventions for the elimination of cancer for all (see **Greater Efforts to Reduce Cancer Health Disparities**, p. 81).

TABLE 3 | **COMPARISON OF FIVE-YEAR SURVIVAL RATES FOR PEDIATRIC CANCERS (0-19 YRS) BETWEEN 1975-79 AND 2003-09**



* Followed through 2010

^ Cancers in children and younger adolescents are classified by histology (tissue type) into 12 major groups using the International Classification of Childhood Cancers (ICCC)

Adapted from Ref. (1)

Stage at diagnosis

affects the 5-year survival for women with breast cancer (1)

89%	99%	84%	24%
Overall	Local	Regional	Distant

Although tremendous progress against cancer has been made see **Table 2**, p. 4 and **Table 3** , p. 6), the number of Americans receiving a cancer diagnosis each year has been increasing steadily for the past four decades, and this number is expected to rise significantly, reaching almost 2.4 million in 2035 (6). This projected increase is largely because cancer is, primarily, a disease of aging. Most cancer diagnoses occur in those age 65 and older (7), and this portion of the U.S. population is expected to double by 2060 (8). High rates of obesity and continued use of tobacco products by 18 percent of adults in the United States (9), both of which are linked to an elevated risk for numerous types of cancer (10, 11), are contributing to the problem.

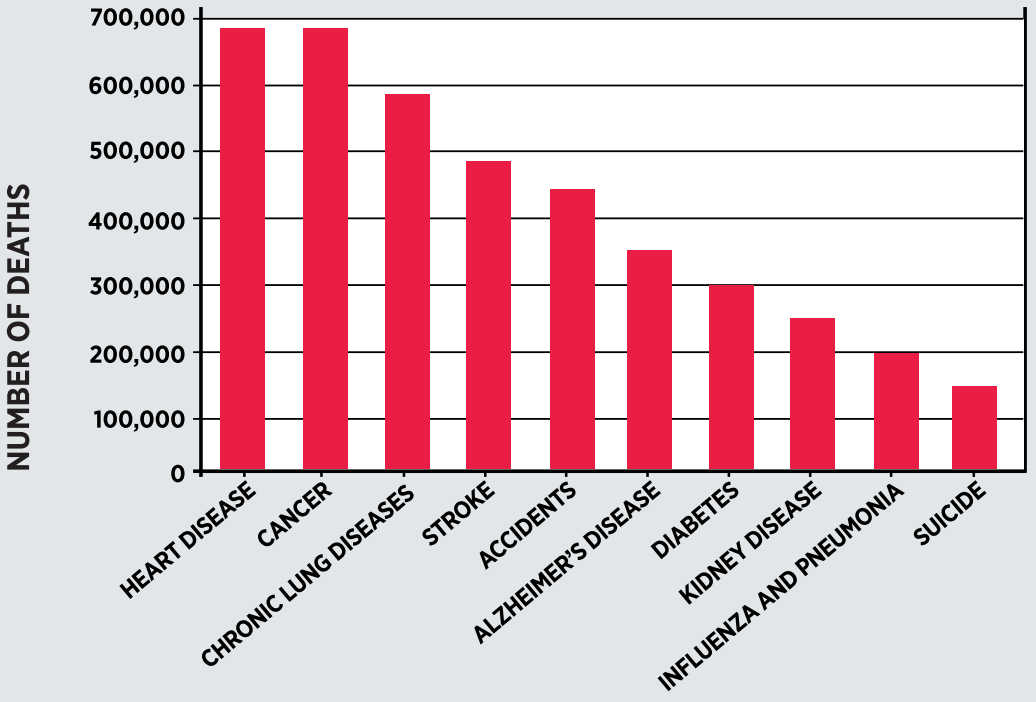
This rise in cancer cases is directly leading to an increase in the number of Americans dying of cancer. In fact, it is estimated that 585,720 people will die from some form of cancer in 2014 (1). Unless more effective strategies for

More than 50%

of cancers are diagnosed in people age 65 or older (7).

FIGURE 2 | **DEADLY DUO**

Together, heart disease and cancer caused approximately half of the 2,468,435 deaths that occurred in the United States in 2010. Moreover, each resulted in more than four times the number of deaths as the third most common cause of death, chronic lung diseases. If current trends continue, cancer will soon overtake heart disease as the leading cause of death for all Americans; it has already done so among the U.S. Hispanic population (13). Data from (12).

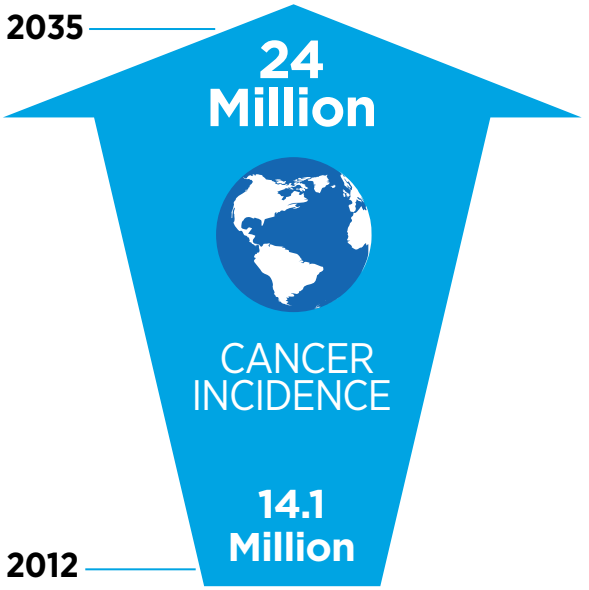


1 in 4

deaths in the United States is due to cancer (1).

cancer prevention, early detection, and treatment can be developed, it will not be long before cancer overtakes heart disease as the leading cause of death for all Americans, as it already is among the U.S. Hispanic population (12, 13) (see **Figure 2**, p. 7).

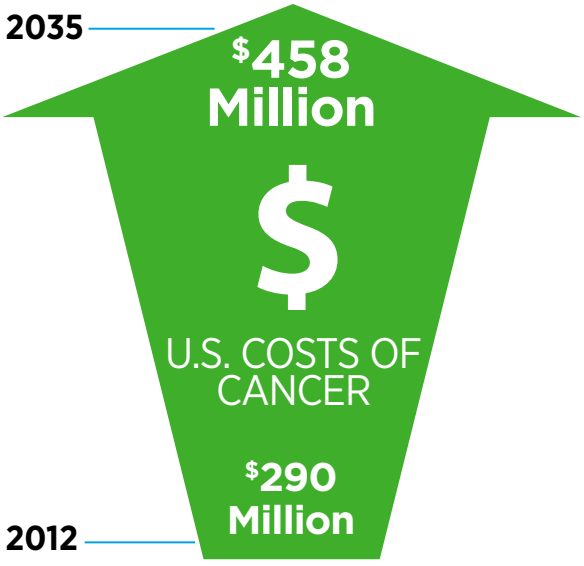
These challenges are not unique to the United States; they are also global problems. In 2012 alone, it is estimated that almost 14.1 million people worldwide received a diagnosis of cancer and 8.2 million died of the disease (6). Without significant new advances in cancer prevention, detection, and treatment, these numbers are projected to rise to 24 million new cancer cases and 14.6 million cancer deaths in 2035.



Cancer: A Costly Disease. Research: A Vital Investment

The immense burden of cancer is clear not just from the large number of lives it touches but also from its significant economic impact. Cancer is among the costliest of diseases to the United States. The most recent NIH estimates indicate that the overall economic costs of cancer in 2009 were $216.6 billion: $86.6 billion in direct medical costs (i.e., the costs for all health expenditures) and $130.0 billion for indirect costs (i.e., costs for lost productivity due to premature death) (1). These costs stand in stark contrast to the NIH and NCI budgets for fiscal year 2014, which are just $30 billion and $4.9 billion, respectively.

The global economic toll of cancer is also enormous. It has been estimated that the 12.9 million new cases of cancer diagnosed in 2009 cost the world $286 billion that year alone (14). As the number of cancer cases rises, so, too, does cost. The 13.3 million new cases of cancer diagnosed worldwide in 2010 are estimated to have cost $290 billion, and the 21.5 million new cancer cases anticipated to occur in 2030 are projected to cost $458 billion (15).



The rising economic and personal burden of cancer underscores the urgent need for more research to develop new prevention and treatment approaches. Recent advances, some of which are highlighted in this report, were made as a direct result of the cumulative efforts of researchers across the spectrum of research disciplines. Much of their work, and the advances that followed, was a direct result of research funding from the federal government. Thus, it is imperative that Congress and the administration increase investments in the primary federal agencies that support this vital research, the NIH and NCI.

DEVELOPING CANCER

IN THIS SECTION YOU WILL LEARN:

- CHANGES IN THE GENETIC MATERIAL IN A NORMAL CELL UNDERPIN CANCER INITIATION AND DEVELOPMENT IN MOST CASES.
- A CANCER CELL'S SURROUNDINGS INFLUENCE THE DEVELOPMENT AND PROGRESSION OF DISEASE.
- THE MOST ADVANCED STAGE OF CANCER, METASTATIC DISEASE, ACCOUNTS FOR MORE THAN 90 PERCENT OF CANCER DEATHS.
- THE MORE WE KNOW ABOUT THE BIOLOGY OF CANCER, THE MORE PRECISELY WE CAN PREVENT, DETECT, DIAGNOSE, AND TREAT IT.

Cancer arises when the orderly processes that control the multiplication and life span of normal cells go awry. As a result, the cells start multiplying uncontrollably, fail to die when they should, and accumulate, either forming a tumor mass in any organ or tissue of the body or crowding out the normal cells in the blood or bone marrow. Over time, tumors can enlarge as more cells accumulate, until some cells gain the ability to invade local tissues and spread, or metastasize, to distant sites (see **Figure 3**). The emergence of metastatic cancer is a dire occurrence that accounts for more than 90 percent of cancer deaths.

The changes in cell behavior that occur during the initiation, development, and progression of a cancer are predominantly a result of changes in the genetic material of the cells. The length of time it takes for a cancer to develop varies widely and depends on the identity, order, and speed at which changes in the genetic material accumulate. Numerous interrelated factors, such as a person's genetic makeup and environmental factors like tobacco use, diet, associated illnesses, and other exposures, also influence this rate.

FIGURE 3 | **HOW BAD IS IT?**

Many cancers are progressive in nature. In the general example depicted here, normal cells first take on precancerous characteristics. As these cells multiply and evolve, the precancerous lesion becomes a tumor that gradually gets larger and extends to lymph nodes as it becomes more advanced, ultimately metastasizing. Assessing the degree to which a patient's cancer has progressed helps doctors select an appropriate treatment and estimate prognosis or predict outcome. Staging is the term used to describe the severity of a person's cancer. Most solid tumors, except for brain and spinal tumors, are staged using the TNM system; gynecological cancers use a variant of the TNM system. The system is based on tumor size (T), reach to local lymph nodes (N), and extent of spread in the body (metastasis; M). Each organ has a specific set of guidelines for determining stage using the TNM system.

Cancer Development: Influences Inside the Cell

The entirety of a person's deoxyribonucleic acid (DNA) is called their genome (see sidebar on **Genetic and Epigenetic Control of Cell Function**). A "mutation" is a change in the type or order of the bases that make up the DNA code. Because a cell reads the DNA code to produce the proteins it needs to function, mutations in the code can result in altered protein amounts or functions (see sidebar on **Genetic Mutations**, p. 11). If these changes alter proteins that control certain critical cell functions, such as cell multiplication or survival, they can ultimately lead to cancer.

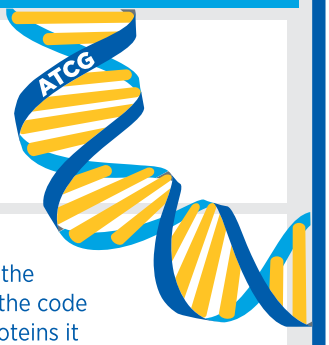
Many different types of mutations can lead to cancer. Over the years, researchers have determined that cancer-associated mutations are most often found in one of two classes of genes: (proto)oncogenes and tumor suppressor genes.

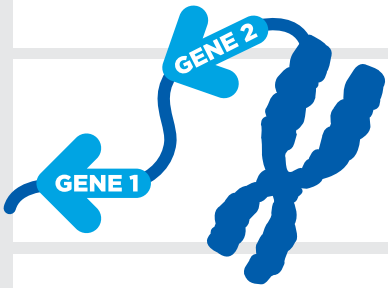
Mutations in (proto)oncogenes lead to altered proteins that can drive the initiation and progression of cancer. Tumor suppressor genes code for proteins that normally repair damaged DNA or repress signals that promote cell survival and multiplication. Alterations in these genes can lead to cancer by permitting the accumulation of harmful DNA mutations or by allowing overactive cells to survive or begin growing again.

In addition to mutations in their DNA, most cancer cells also have profound abnormalities in their epigenomes when compared with normal cells of the same tissue. In many cases, these epigenetic defects work in conjunction with permanent

GENETIC AND EPIGENETIC CONTROL OF CELL FUNCTION

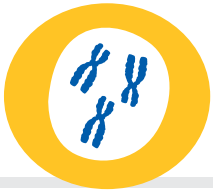
The genetic material of a cell is comprised of strings of four **deoxyribonucleic acid (DNA)** units called bases.





DNA bases are organized into **genes**, and 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 their body contains a copy of their genome. The genome is packaged together with proteins known as histones into structures called **chromosomes.**



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

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

changes in the DNA of the cell to promote cancerous behaviors. One of the most exciting recent discoveries is that some epigenetic abnormalities may be reversible.

Cancer Development: Influences Outside the Cell

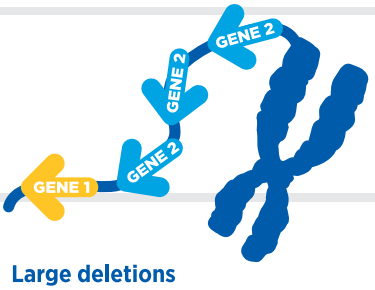
It is clear that cancer develops as a result of alterations to the genetic material of a cell that lead to malfunctions in its behavior. Research has revealed, however, that interactions between cancer cells and their environment—known as the tumor microenvironment—as well as interactions with systemic factors, are an important part of cancer development (see sidebar on **Cancer Growth: Local and Global Influences**, p. 12). This means that cancer is much more complex than an isolated mass of proliferating cancer cells. Therefore, if we are to advance our mission to prevent and cure all cancers, we must develop a more comprehensive, whole-patient understanding of cancer.

90%
of cancer deaths are a result of **metastasis**.

GENETIC MUTATIONS

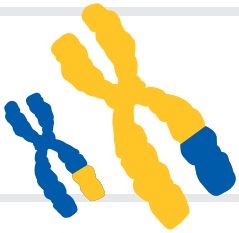
Below are some of the various genetic mutations known to lead to cancer; however, genetic mutations do not always result in cancer.

Single base changes
- Some mutations can lead to new proteins that may cause cancer to develop.
- Deletion or insertion of DNA sequences can lead to new proteins or loss of protein function that can lead to cancer.



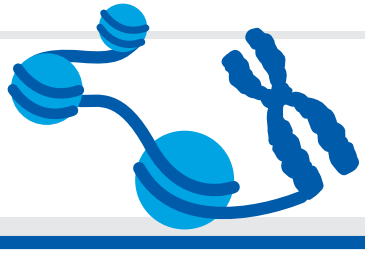
Extra copies of genes (gene amplification)
Higher quantities of certain proteins can lead to enhanced cell survival and growth, leading to cancer.

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
Mutations in the genes that produce proteins that alter the epigenetic marks on DNA or the histones around which it is packaged can lead to cancer.



Some components of the tumor microenvironment are normal parts of the tissue in which the cancer is growing. Others are systemic factors that transiently affect the tumor microenvironment as they percolate through it. Yet others are actively recruited or formed as a result of signals emanating from the cancer cells themselves. Whether passive participants or active recruits, the various components of the microenvironment are often exploited by cancer cells to advance their growth and survival.

Cancer Development: Exploiting Our Expanding Knowledge to Improve Health Care

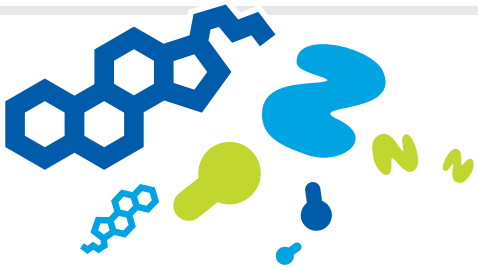
Fundamental research expands our knowledge of the biology of cancer (see sidebar on **Fundamental Research: The Foundation of Today's Treatments and Tomorrow's Advances**, p. 13). As our knowledge has grown, so has our ability to exploit it to develop new and improved approaches to cancer prevention, detection, diagnosis, and treatment.

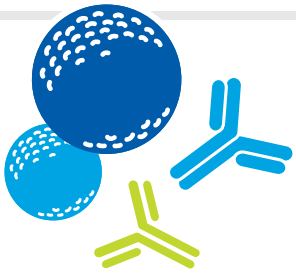
CANCER GROWTH: LOCAL AND GLOBAL INFLUENCES

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

The majority of the new approaches more precisely attack cancers than do traditional therapies, providing patients with not just longer but also higher-quality lives.

It is clear that, through this fundamental research, which is largely supported by the NIH and NCI, we have developed a greater understanding of the processes by which cancer starts, progresses, and results in disease. This knowledge has yielded significant progress in preventing, detecting, diagnosing, and treating cancer. Continued progress, therefore, will be made only through additional research, and as such, it is imperative that the administration and Congress support the primary federal agencies that support this vital research, the NIH and NCI.

FUNDAMENTAL RESEARCH: THE FOUNDATION OF TODAY'S TREATMENTS AND TOMORROW'S ADVANCES

45
FDA-APPROVED THERAPIES

A more comprehensive understanding of the genetic and molecular underpinnings of normal and tumor cell biology has led to the development of **45 FDA-approved therapies that target specific molecules involved in cancer.**

5
FDA-APPROVED THERAPIES

An understanding that epigenetic factors influence cancer development has led to **five FDA-approved therapies that work by targeting the proteins that modify the epigenome**, with more under development, such as the therapy Jack Whelan received (see p. 36).

10
ANTICANCER THERAPIES

Identification of the factors and processes by which cancer cells stimulate the development of blood and lymphatic vessel networks has led to **10 anticancer therapies** that impede this process.

17
ANTIHORMONE THERAPIES

Knowledge that the hormones estrogen and testosterone are systemic factors that drive many breast and most prostate cancers, respectively, led to the development of **17 antihormone therapies** to treat patients with these diseases.

A more complete understanding of the immune system and its function has led to the development of a class of treatments collectively known as immunotherapies. These revolutionary treatment approaches harness a patient's own immune system to eliminate their cancer cells. They were highlighted in the *AACR Cancer Progress Report 2013 (5)*, and they are discussed here in **Treatment With Immunotherapeutics** (see p. 64).

HEALTHY LIVING CAN PREVENT CANCER FROM DEVELOPING, PROGRESSING, OR RECURRING

IN THIS SECTION YOU WILL LEARN:

- MORE THAN HALF OF CANCER DEATHS IN THE UNITED STATES ARE A RESULT OF PREVENTABLE CAUSES.
- TOBACCO USE IS RESPONSIBLE FOR ALMOST 30 PERCENT OF CANCER DEATHS IN THE UNITED STATES.
- ULTRAVIOLET RADIATION FROM THE SUN AND INDOOR TANNING DEVICES CAUSES THE MAJORITY OF SKIN CANCERS.
- DEVELOPING A PERSONALIZED CANCER-SCREENING PLAN WITH YOUR PHYSICIANS IS PART OF A HEALTHY APPROACH TO LIVING.
- ABOUT ONE IN EVERY FIVE CANCER DIAGNOSES WORLDWIDE IS ATTRIBUTABLE TO PERSISTENT INFECTION WITH A PATHOGEN. INFECTION WITH MANY KNOWN CANCER-CAUSING PATHOGENS CAN BE PREVENTED BY VACCINATION OR TREATMENT WITH MEDICINES.
- UP TO ONE-THIRD OF ALL NEW CANCER DIAGNOSES IN THE UNITED STATES ARE RELATED TO BEING OVERWEIGHT OR OBESE, PHYSICAL INACTIVITY, AND/OR POOR DIETARY HABITS.

Many of the greatest reductions in cancer morbidity and mortality are a result of advances in cancer prevention and early detection. These advances were enabled by translating the discoveries of the causes and progressive nature of cancer into effective new clinical practices and public education and policy initiatives.

Central to preventing cancer is the identification of factors that increase a person's risk of developing cancer and eliminating or reducing these factors where possible (see **Figure 4**, p. 15). As research has enhanced our knowledge of cancer risk factors, we have learned that more than 50 percent of the 585,720 cancer deaths expected to occur in the United States in 2014 will be related to preventable causes (16).

Many factors that increase the risk of developing cancer are related to lifestyle; thus, adopting a healthy approach to living, where possible, can eliminate or reduce the risk of some cancers (see **Figure 5**, p. 15). Moreover, many healthy approaches to living can also reduce cancer recurrence and improve outcomes following a cancer diagnosis. However, a great deal more research and many more resources are needed to understand how best to help individuals change their lifestyle.

Adopting Healthy Approaches to Living

Tobacco use is responsible for almost 30 percent of cancer deaths each year in the United States (1) (see **Figure 6**, p. 16). As a result, one of the most effective ways a person can lower the risk of developing cancer is to eliminate tobacco use (see sidebar on **Reasons to Eliminate Tobacco Use**, p. 17). This relationship between tobacco use and cancer was first brought to the public's attention 50 years ago, when the U.S. Surgeon General's report on "Smoking and Health" was published (17). Since then, smoking rates among U.S. adults have more than halved, and as a result, an estimated 800,000 deaths from lung cancer were avoided between 1975 and 2000 (18).

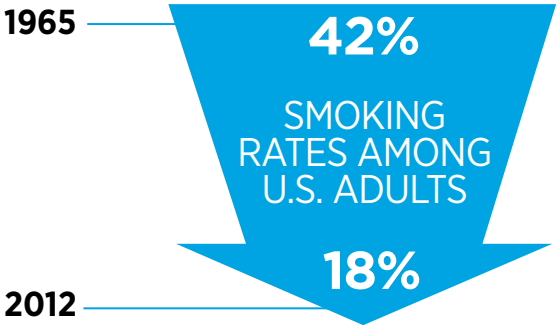
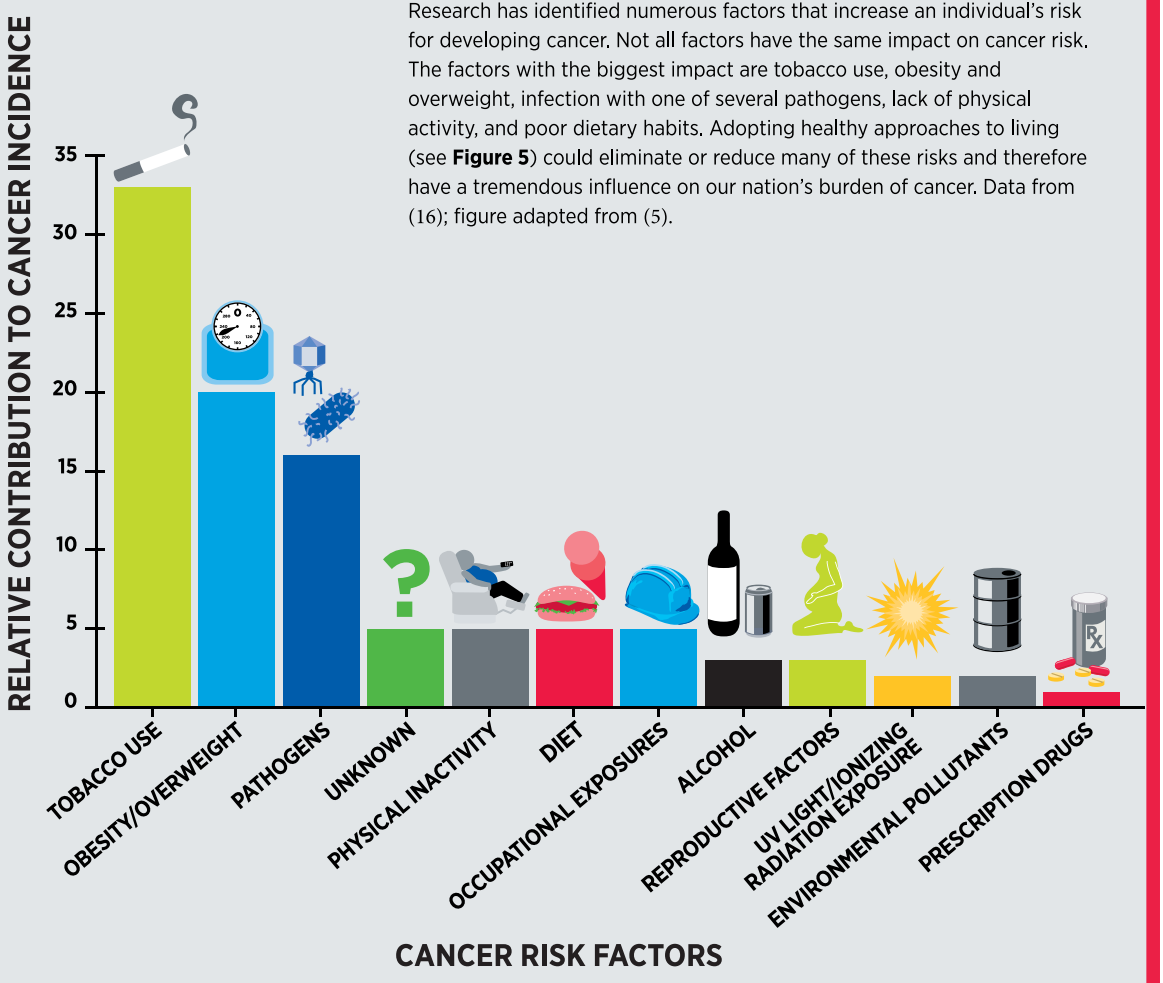


FIGURE 4 | **RISKY BUSINESS**

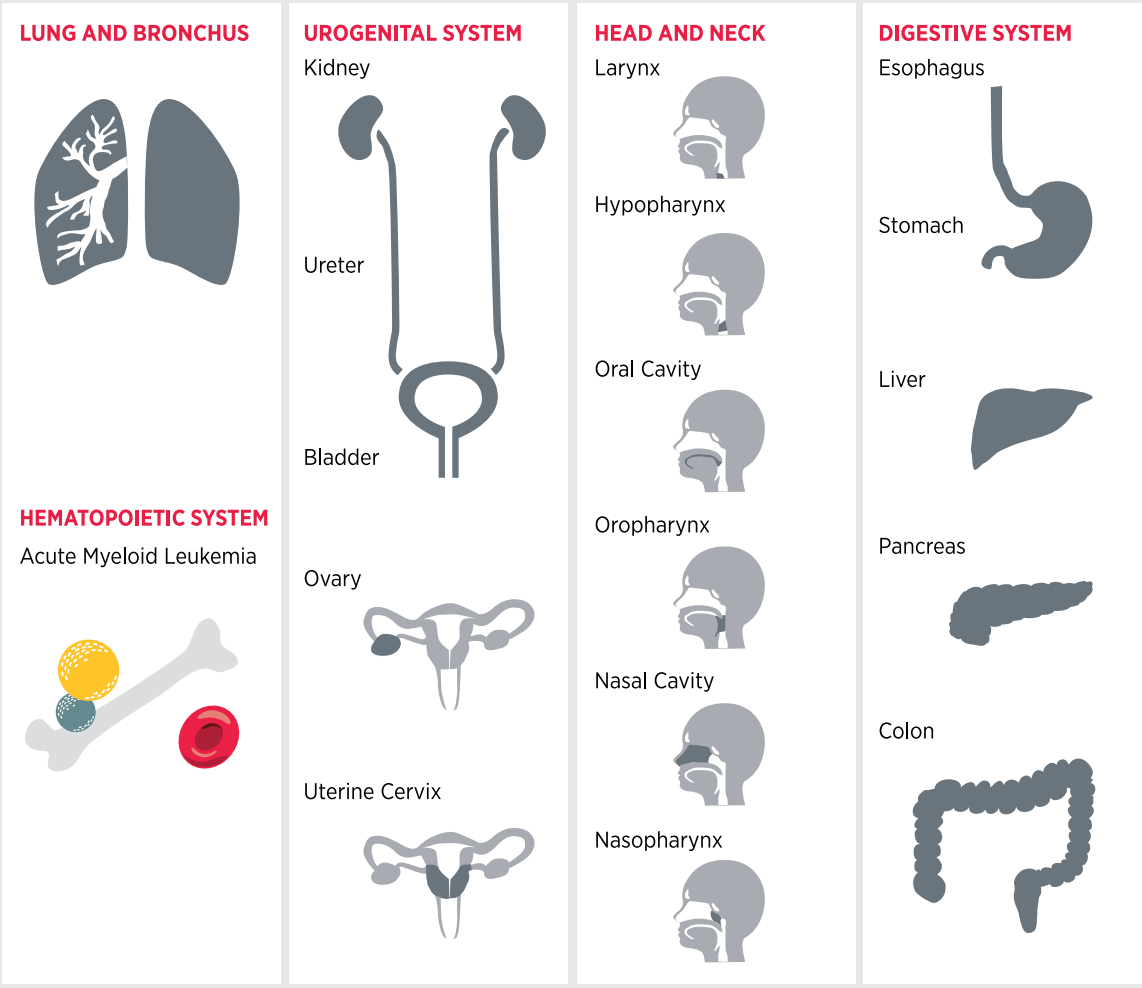


Research has identified numerous factors that increase an individual's risk for developing cancer. Not all factors have the same impact on cancer risk. The factors with the biggest impact are tobacco use, obesity and overweight, infection with one of several pathogens, lack of physical activity, and poor dietary habits. Adopting healthy approaches to living (see **Figure 5**) could eliminate or reduce many of these risks and therefore have a tremendous influence on our nation's burden of cancer. Data from (16); figure adapted from (5).

FIGURE 5 | **HEALTHY APPROACHES TO LIVING**

Research has identified numerous factors that affect a person's risk of developing cancer (see **Figure 4**). Many of the factors with the greatest influence on cancer risk can be eliminated or reduced by adopting a healthy approach to living. For example, ending tobacco use, eating a healthy and balanced diet, undertaking regular physical activity, reducing exposure to the sun, managing pre-existing medical conditions with the appropriate medications, getting vaccinated against certain pathogens, and developing a personalized cancer screening program with a physician (or physicians) are all part of a healthy approach to living.

FIGURE 6 | **BEYOND THE LUNGS: CANCERS CAUSED BY TOBACCO USE**



Tobacco use increases an individual's risk of developing not only lung cancer but also 17 other types of cancer (11). This explains why tobacco use will account for an estimated 30 percent of all cancer deaths in the United States in 2014 (1).

Unfortunately, the rate of decline in smoking prevalence in the United States has slowed in recent years (18). In fact, almost 70 million individuals age 12 or older are regular users of tobacco products (20).

778,000

Americans age **12 or older** began smoking cigarettes daily in 2012 (20).

If we are to eradicate one of the biggest threats to public health, researchers, clinicians, advocates, and policymakers must continue to work together. Several steps that could be taken to achieve this goal are outlined in this year's Surgeon General's report, "The Health Consequences of Smoking—50 Years of Progress," (see sidebar on **Eliminating Tobacco Use Faster**, p. 93) (18). Of particular importance is the regulation of additional tobacco products by the FDA.

Other healthy approaches to living that can significantly reduce cancer risk are maintaining a healthy weight, which is defined as a body mass index (BMI) between 18.5 and 24.9 kg/m^2 for adults over 20 years of age; keeping active; and eating a balanced diet (see sidebar on **Reasons to Maintain a Healthy Weight and Keep Active**, p. 18). The

REASONS TO ELIMINATE TOBACCO USE

20 MILLION DEATHS

More than 20 million people in the United States died prematurely as a result of smoking and exposure to secondhand smoke between 1965 and 2014 (18).

18 TYPES OF CANCER

Eighteen types of cancer are causally related to tobacco use (see **Figure 6,** p. 16) (11).

0 EXPOSURE

No level of exposure to tobacco smoke is safe, including exposure to secondhand smoke (19).

6.5 MILLION SMOKING-RELATED DEATHS

Between 1965 and 2014, more than 6.5 million Americans died of a smoking-related cancer and more than 250,000 died of lung cancer caused by exposure to secondhand smoke (18).

Tobacco use during chemotherapy can reduce the effectiveness of treatment.

In addition to cancer-related deaths, tobacco exposure caused nearly 10 million cardiovascular and metabolic disease-related deaths between 1965 and 2014 (18).

Eliminating tobacco use after a cancer diagnosis can reduce the complications associated with treatment and improve overall survival.

impact of adopting these aspects of a healthy lifestyle could be enormous because it is estimated that one-third of all new cancer diagnoses in the United States are related to being overweight or obese, not getting enough physical activity, and/or having poor dietary habits (10, 16). Moreover, more than one-third of adults, or more than 72 million individuals, and 17 percent of youth in the United States are obese (21, 22).

Body Mass Index (BMI)

[weight in kilograms divided by height in meters squared]

underweight: BMI less than 18.5 kg/m^2

overweight: BMI between 25 and 29.9 kg/m^2

obese: BMI over 30 kg/m^2

REASONS TO MAINTAIN A HEALTHY WEIGHT AND KEEP ACTIVE

33%
CANCER CASES

About one in every three new cases of cancer diagnosed in the United States is related to being overweight or obese, being inactive, and/or eating poorly (10, 16).

The adenocarcinoma subtype of esophageal cancer, colorectal, endometrial, gallbladder, kidney, pancreatic, and postmenopausal breast cancers have been causally linked to being overweight or obese (10).

7
TYPES OF CANCER

Regular physical activity can decrease an individual's risk of developing colon, endometrial, and postmenopausal breast cancers (23).

Sedentary behavior may increase the risk for developing colorectal, endometrial, ovarian, and prostate cancers (24).

Obesity, lack of regular physical activity, and sedentary behavior are linked to worse outcomes, including increased risk for death, for patients with a number of types of cancer.

Fortunately, regular physical activity, independent of body fatness, can decrease the risk of developing certain cancers (23). However, nearly half of adults in the United States do not meet the recommended guidelines for aerobic physical activity (25) (see sidebar on **Physical Activity Guidelines**, p. 19). Moreover, sedentary behavior, independent of body mass and periodic physical activity, can increase the risk of developing certain types of cancer (24).

Sedentary behaviors

involve prolonged sitting or lying down and a lack of whole-body movement, e.g. sitting at a computer. They are not the same as physical inactivity, which is a lack of physical activity in everyday life.

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 like running daily.

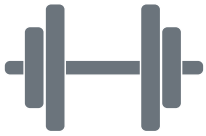
Muscle- and bone-strengthening exercises like pushups daily or at least three days per week.

FOR ADULTS

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

At least 150 minutes per week of moderate-intensity activity like a brisk walk or 75 minutes of vigorous-intensity activity, like running, in a week.

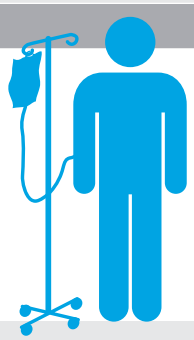
Moderate- or high-intensity muscle-strengthening activities two or more days per week.



FOR SPECIFIC POPULATIONS

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

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



Realization of the enormity of personal and financial health care problems resulting from overweight and obesity, lack of physical activity, and/or poor dietary habits has led to some progress in recent years. For example, the proportion of U.S. adults who walk for transportation, fun, or exercise rose 6 percent from 2005 to 2010 (26). In addition, when considering the U.S. population as a whole, the prevalence of obesity has remained stable since 2003 (21). However, this is not true for all segments of the population.

Beyond preventing the development of some cancers, following the physical activity guidelines may also improve outcomes for individuals diagnosed with certain types of cancer, in particular breast, colorectal, and prostate cancers; reduce risk of disease recurrence and metastasis; and increase the chance of long-term survival (27-29).

Although small improvements in maintaining a healthy weight and increasing physical activity have been made, more action is urgently needed. Concerted efforts by individuals, families, communities, schools, workplaces and institutions, health care professionals, media, industry, government, and multinational bodies are required to develop effective and comprehensive strategies to promote the maintenance of a healthy weight and the participation in regular physical exercise. One new strategy, Park Rx, an

initiative of the National Park Service, seeks to encourage health care providers to help patients establish an exercise routine by effectively using their neighborhood parks.

Another way that individuals can reduce their risk of developing cancer, specifically the three main types of skin cancer—basal cell carcinoma, squamous cell carcinoma, and melanoma—is by limiting their exposure to ultraviolet (UV) radiation (see sidebar on **Reasons to Protect Your Skin**). In fact, the International Agency for Research on Cancer (IARC), an affiliate of the World Health Organization, considers exposure to UV radiation from any source as "carcinogenic to humans" (30), alongside agents such as plutonium and cigarettes.

Despite this, half of all adults in the United States report at least one sunburn in the past 12 months and 5 percent report using a UV indoor tanning device at least once, with many using these devices 10 or more times a year (37, 38). Moreover, 13 percent of all high school students and 21 percent of high school girls report using an indoor UV tanning device in the past year (39).

Given that many cases of skin cancer are preventable, it is important that everyone work together to develop and implement more effective policy changes and public education campaigns to help reduce the health and economic burdens of the disease. For example, initiatives aimed at increasing the number of individuals who adopt

REASONS TO PROTECT YOUR SKIN

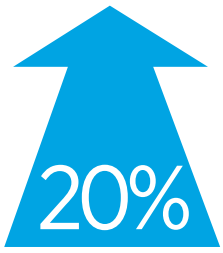
Exposure to ultraviolet (UV) radiation from the sun, sunlamps, sunbeds, and tanning booths is the predominant cause of the three main types of skin cancer.

Melanoma incidence rates have been on the rise for at least 30 years (1).

More than 85 percent of all skin cancers are estimated to be due to UV radiation exposure from the sun (31, 32).

85%
SKIN CANCERS

Use of a UV indoor tanning device increases melanoma risk by 20 percent, and each additional use increases risk a further 1.8 percent (34).



In the United States, 8 percent of all melanoma cases each year have been attributed to indoor tanning (33).

8%
MELANOMA CASES

Regular, daily use of sunscreen (sun protection factor [SPF] of 15 or higher) reduces an individual's risk of developing squamous cell carcinoma and melanoma by 40 percent and 50 percent, respectively (35, 36).

NO restrictions

on tanning bed use exist in Alaska, Colorado, Hawaii, Idaho, Kansas, Missouri, Montana, New Mexico, Oklahoma, Pennsylvania, South Dakota, or Washington.

sun-safe habits and tighter regulation of indoor tanning would dramatically reduce the incidence of skin cancer (see sidebar on **Sun-safe Habits**).

Persistent infection with a number of pathogens—bacteria, viruses, or parasites that cause disease—can result in certain types of cancer (40, 41) (see **Table 4**, p. 22). In fact, pathogens are estimated to cause about 2 million cancer cases each year, 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 papilloma virus (HPV) (42) (see **Figure 7**, p. 23).

This knowledge has enabled the development of strategies to eliminate or prevent infection with these cancer-associated pathogens (see sidebar on **Cancer-causing Pathogens: Prevention and Elimination**, p. 24). Consulting with a physician and following his or her advice regarding the use of these strategies can reduce an individual's risk of certain cancers and is part of a healthy approach to living.

Hepatitis C virus

causes more deaths in the United States than HIV/AIDS (43).

SUN-SAFE HABITS

To reduce your risk of skin cancer, the Centers for Disease Control and Prevention recommend that you:

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

- cover up with clothing that covers your arms and legs;

- wear a wide-brimmed hat;

- wear wrap-around sunglasses; and

- apply a sunscreen rated sun protection factor (SPF) 15 or higher at least every two hours.

TABLE 4 | **INFECTIOUS CAUSES OF CANCER**

BACTERIA

Pathogen	Cancer
Helicobacter pylori	Stomach cancers

PARASITES

Pathogen	Cancer
Clonorchis sinensis	Biliary cancer, pancreatic cancer, and gallbladder cancer
Opisthorchis viverrini	Biliary cancer, pancreatic cancer, and gallbladder cancer
Schistosoma haematobium	Bladder cancer

VIRUSES

Pathogen	Cancer
Epstein-Barr Virus (EBV)	Stomach cancers, Hodgkin and non-Hodgkin lymphomas, and nasopharyngeal cancers
Hepatitis B/C Virus (HBV and HCV)	Hepatocellular carcinoma
Human Immunodeficiency Virus (HIV)	Kaposi sarcoma and non-Hodgkin lymphoma
Human Papillomavirus (HPV)	Cervical, anogenital, head and neck, and oral cancers
Human T-cell Lymphotrophic Virus, type 1 (HTLV-1)	T-cell leukemia and lymphoma
Merkel Cell Polyomavirus (MCV)	Skin cancer

Despite the availability of strategies to eliminate or prevent infection with some cancer-associated pathogens, researchers estimate that pathogen-related cancers account for about 20 percent of cancer diagnoses worldwide (40) (see **Figure 7**, p. 23). Thus, it is clear that these strategies are not being used optimally and that a dramatic reduction in the global cancer incidence could be achieved by more effective implementation. In fact, the CDC estimates that in 2012, only 33 percent of girls ages 13–17 in the United States had received the recommended three doses of HPV vaccine (60). Moreover, this percentage varies widely among states, with fewer than 26 percent of girls completing the vaccine course in six states, and the lowest rate being just 12.1 percent (44). Further, the "President's Cancer Panel 2012–2013 Report" stated that in the United States alone, more than 50,000 cases of cervical cancer and thousands of cases of other types of cancer could be prevented if 80 percent of those for whom the HPV vaccine is recommended—girls and boys ages 11 and 12, respectively—were to be vaccinated (44) (see sidebar on **The "President's Cancer Panel Report,"** p. 25).

12 Strains of HPV Cause Cancer (61).

(HPV16, -18, -31, -33, -35, -39, -45, -51, -52, -56, -58, and -59)

FIGURE 7 | **CATCHING A CAUSE OF CANCER**

Persistent infection with a number of pathogens is estimated to cause approximately 2 million cases of cancer worldwide each year (42) (see **Table 4**, p. 22). More than 90 percent of these cases are attributable to just four pathogens—*Helicobacter pylori*, hepatitis B virus (HBV), hepatitis C virus (HCV), and human papillomavirus (HPV). Each pathogen is linked with a specific type of cancer or cancers, and strategies exist to eliminate or prevent infection with some of these cancer-associated pathogens. It is clear, however, that a dramatic reduction in the global incidence of these types of cancer could be achieved by more effective implementation of such strategies. Data from (42-49); figure adapted from (50).

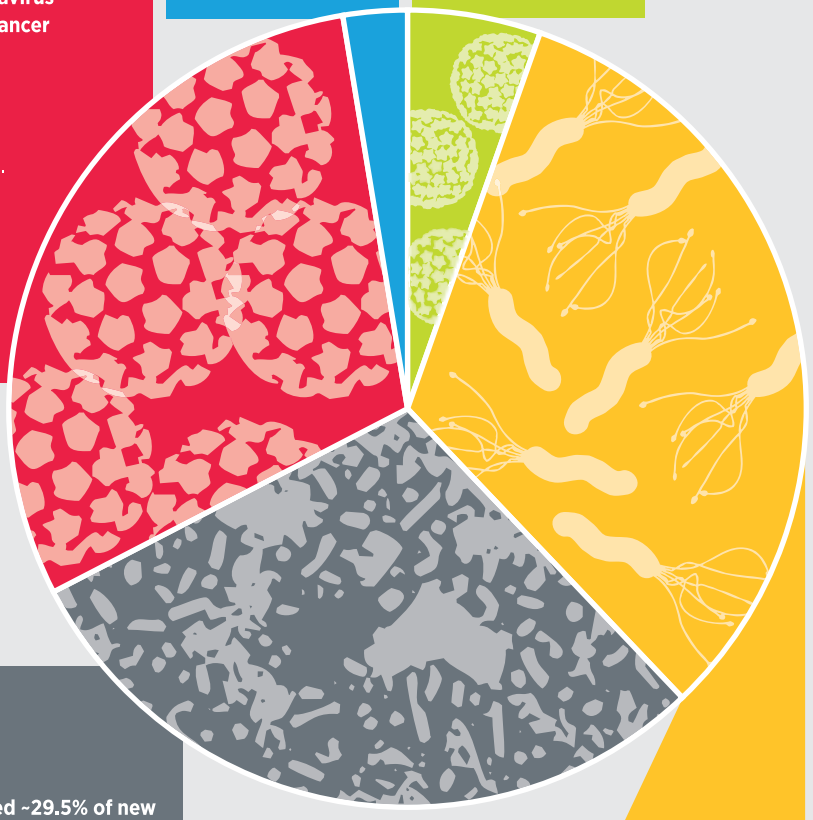
HPV 30.0%

12 strains of human papillomavirus (HPV) caused ~30% of new cancer cases attributed to infection globally in 2008.

In the United States:
~96% of cervical cancer cases.
~51% of vulvar cancers.
~64% of vaginal cancers.
~36% of penile cancers.
~93% of anal cancers.
~63% of oropharyngeal head and neck cancers.

Other Agents 2.6%

Epstein-Barr Virus (EBV) 5.4%



HBV and HCV 29.5%

HBV and HCV infection caused ~29.5% of new cancer cases attributed to infection globally in 2008.

Hepatitis B virus (HBV):
Causes ~45% of of liver cancer deaths worldwide.

Over 700,000 individuals in the United States are estimated to be infected with HBV.

Hepatitis C virus (HCV):
Causes ~25% of liver cancer deaths worldwide.
~2.7 million individuals in the United States are infected with HCV and unaware.

Helicobacter pylori 32.5%

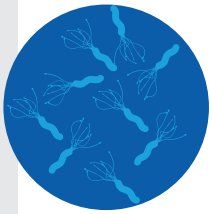
***Helicobacter pylori* causes:**

~32.5% of new cancer cases attributed to infection globally in 2008.

~90% of lower gastric (stomach) cancers.

~86% of cases of gastric mucosa-associated lymphoid tissue (MALT) lymphoma.

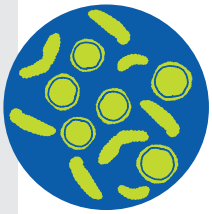
CANCER-CAUSING PATHOGENS: PREVENTION AND ELIMINATION



HELICOBACTER PYLORI

Helicobacter pylori infection can be eliminated by treatment with a combination of stomach-acid suppressants and antibiotics (51).

The Centers for Disease Control and Prevention (CDC) recommends testing and treatment for those with active or a documented history of gastric or duodenal ulcers, low-grade gastric mucosa-associated lymphoid tissue (MALT) lymphoma, or early gastric cancer that has been surgically treated.

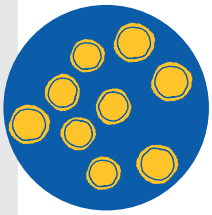


HEPATITIS B VIRUS (HBV)

Infection with HBV can be prevented by vaccination, which has been part of the routine childhood immunization schedule since 1991 (52).

Treatment with antiviral drugs can eliminate HBV in those chronically infected with the virus (53).

The U.S. Preventive Services Task Force (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 (54).

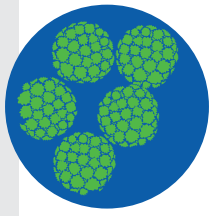


HEPATITIS C VIRUS (HCV)

The antiviral drugs sofosbuvir (Solvadi) and simeprevir (Olysio) are two new HCV treatment options recently approved by the FDA.

Numerous antiviral drug combinations that exclude interferon, a mainstay of HCV treatment, are in clinical trials and show efficacy in more than 90 percent of patients (55).

The CDC and USPSTF recommend screening those born from 1945 to 1965 for HCV infection (56).



HUMAN PAPILLOMAVIRUS (HPV)

Two FDA-approved vaccines can protect against infection with HPV16 and HPV18.

Both vaccines are highly effective at preventing precancerous cervical lesions (57, 58).

One of the vaccines, Gardasil, was also found to prevent precancerous anal, vulvar, and vaginal lesions (58, 59).

According to the CDC, safe sex practices may lower the risk of, but may not fully protect against, HPV infection.

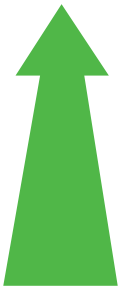
THE "PRESIDENT'S CANCER PANEL REPORT"

As part of the National Cancer Act of 1971, a three-person panel was created to report to the president of the United States on the development and execution of the National Cancer Program and make recommendations for improvements. Members of the President's Cancer Panel are invited to serve a three-year term, and at least two panel members must be distinguished scientists or physicians.

The "President's Cancer Panel Report 2012–2013" detailed progress against cancers caused by persistent infection with human papillomavirus (HPV), and **recommended the following to increase vaccine uptake** (44):

reduce missed clinical opportunities to recommend and administer HPV vaccines;

increase parents', caregivers', and adolescents' acceptance of HPV vaccines; and



maximize access to HPV vaccination services.

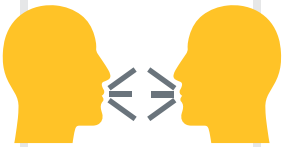
The panel also recommended **the following areas of research to promote global HPV vaccine uptake**:

investigating more convenient dosing schedules for current vaccines;

developing next-generation vaccines that provide broader protection and/or are easier to store and administer;

explaining the natural history of oropharyngeal HPV infections;

developing more effective ways to communicate about HPV-associated diseases and HPV vaccines; and



determining how best to integrate HPV vaccination with cervical cancer screening.

Research has provided and continues to increase our knowledge of the causes of cancer and the timing, sequence, and frequency of the genetic, molecular, and cellular changes that drive cancer initiation and development. This knowledge provides us with unique opportunities for developing ways to prevent cancer onset or to detect a cancer and intervene earlier in its progression. Finding a cancer early, as **Congressman Ron Barber** (see p. 26) did in 2012, before it has spread to other parts of the body, makes it more likely that a patient can be treated successfully. Cancer screening is therefore an important part of a healthy lifestyle.

FREE OF ORAL CANCER THANKS TO EARLY DETECTION

I was diagnosed with oral cancer just a few days after election night in November 2012. I was extremely fortunate that my cancer was caught early, at stage 1. This meant that the only treatment I needed was surgery to remove the tumor and that my outlook is very good. My experience taught me that it is vital that you pay attention to what your body is telling you and that you don't delay getting anything unusual checked out.

It was the fall of 2012 when I noticed what seemed like a blister on my tongue that didn't heal quickly. I tried a number of topical treatments, but it just wasn't going away so my dentist sent me to an oral surgeon to have it biopsied.

I received the biopsy results at an extremely stressful time—seven days after election night, which was during the 11 days it took to complete the vote count for my district, the 2nd Congressional District of Arizona.

I immediately contacted the University of Arizona Cancer Center in Tucson, which is one of the country's premier cancer centers. Fortunately, the center had recently established an ENT [ear, nose, and throat] team specializing in the treatment of cancers like mine, so I felt I was in the best place possible.

The medical team told me that because my cancer had been caught at an early stage, I should have surgery as soon as possible and that I would need regular follow-up visits. My tumor was removed just before Thanksgiving, and I was fully recovered in time to be sworn into my first full term in Congress on Jan. 3, 2013.

For the first year after surgery, I had follow-ups with my ENT oncologist at the University of Arizona Cancer Center every four weeks, but now it is every eight weeks. My doctors say we could probably go longer between visits, but to be on the safe side they want to continue with this schedule. They also tell me that if anything changes at all I should call and be seen right away, so I keep a pretty constant watch on what's going on. Every now and again, if I bite my tongue or have a little sore, I'll go and be checked, but it has always turned out to be nothing.

One of the things that helped me to get through my experience, other than my fantastic specialty medical team, was the enormous support I got from my wife, my children, my grandkids, and my friends. Sometimes it is hard to ask for help or to accept it, but when you are dealing with a disease like cancer, you really can't hold back—you just have to welcome the support, and I got plenty of it.

By sharing my story, I hope to remind everyone, in particular my colleagues in Congress, that cancer is not an abstract national problem but something that can happen to anybody in the blink of an eye. We are all susceptible. I tend to be kind of stoic, but the truth is that inside I was thinking, is this going to be the beginning of the end? What I learned, though, was that our knowledge about cancer is growing and we have so much good research, and more to come, that I hope it is the beginning of pathways to prevention, treatment, and cure. But to achieve these goals, we need to stay on the cutting edge, and to do this we need more funding for the National Institutes of Health.

THE HONORABLE RON BARBER
(D-ARIZ.)
AGE 69
TUCSON, ARIZONA

"It is vital that you pay attention to what your body is telling you and that you don't delay getting anything unusual checked out."

Over 42,000 individuals in the United States are expected to develop **cancer of the oral cavity or pharynx** (mouth and upper throat) in 2014.

©2014 AACR/Karen Sayre

Screening to detect cancer in individuals showing no signs or symptoms of the disease they are being screened for can have tremendous benefits (see sidebar on **Cancer Screening**). However, it can also cause unintended harm, and this has made it difficult to develop strategies for screening for the majority of cancer types. For a screening program to be successful, it must meet two important criteria: It must decrease deaths from the screened cancer, and the benefits it provides must outweigh any harms. Determining whether a screening program meets these criteria requires an enormous amount of research and careful analysis of the data generated.

CANCER SCREENING

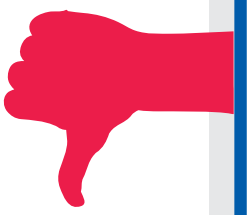
BENEFITS OF SCREENING

Reduced cancer incidence. Screening tests can detect precancerous lesions. Removal of the abnormal tissue can reduce, or even eliminate, an individual's risk of developing the screened cancer. For example, the Pap test can detect lesions before they develop into cervical cancer.

Reduced incidence of advanced disease. Screening tests that detect cancers that have already developed 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.

Reduced mortality. Diagnosis at an early stage of disease increases the likelihood that a patient can be successfully treated, and thereby reduces the individual's risk of dying of the screened cancer. For example, mammography can detect breast cancers at an early stage, when surgery may be curative.

POTENTIAL RISKS OF SCREENING



Adverse Events. Screening tests are medical procedures; as a result, they carry some risk. However, the chance that an adverse event will occur during a screening test approved by the USPSTF 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 tests. Not all individuals who have a positive screening test have the screened cancer. The rates of false-positive tests are generally low, but a false-positive screen can result in additional unnecessary medical procedures, treatments, and anxiety.

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

Overtreatment and overdiagnosis. Not all cancers detected by screening will go on to cause symptoms and threaten life. Overdiagnosis, as this is called, leads to overtreatment, which carries its own risks. The rates of overdiagnosis and overtreatment vary between screening tests and are difficult to quantify.

In the United States, an independent group of experts convened by the Public Health Service rigorously evaluates clinical research to make evidence-based recommendations about clinical preventive services, including cancer-screening tests. These experts form the U.S. Preventive Services Task Force (USPSTF). As of Aug. 1, 2014, the USPSTF recommended that certain segments of the general population be screened for just four types of cancer (see sidebar on **USPSTF Cancer-screening Recommendations**, p. 29). In addition to considering evidence regarding potential new screening programs, the USPSTF routinely evaluates new research regarding established screening programs, and can revise recommendations if deemed necessary.

In the United States, colorectal cancer screening (62):

has helped dramatically reduce colorectal cancer incidence and mortality.

is only used by 59 percent of people for whom it is recommended.

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

USPSTF CANCER-SCREENING RECOMMENDATIONS

Below are the USPSTF recommendations related to population-based screening for early detection of several cancers as of July 31, 2014. Not listed are the screening programs for which the USPSTF believes there is insufficient evidence to make a recommendation. These recommendations do not take into account an individual's unique medical history and risk; thus, everyone should always consult his or her physician prior to making any decision regarding cancer screening.

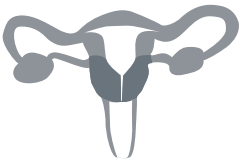
BREAST CANCER

As of November 2013, the USPSTF recommended*:

Women ages 50–74 have a screening mammography once every two years.

Women younger than 50 should make a decision in concert with their physician about when to start regular screening after taking into account their own personal situation.

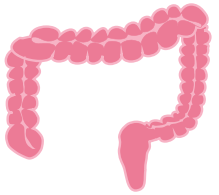
*Breast cancer screening guidelines are currently under review and will be updated in the near future.



CERVICAL CANCER

Women ages 21–29 should have a Pap test every three years.

Women ages 30–65 should have either a Pap test every three years or a Pap test and human papillomavirus (HPV) testing every five years.

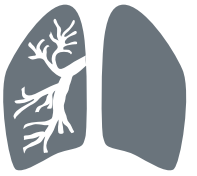


COLORECTAL CANCER

As of January 2014, the USPSTF recommended**:

Adults ages 50–75 should be screened through fecal occult blood testing yearly, sigmoidoscopy every 5 years, or colonoscopy every 10 years.

**Colorectal cancer screening guidelines are currently under review and will be updated in the near future.



LUNG CANCER

As of December 2013, the USPSTF recommended:

Adults ages 55–79 who have smoked 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, should be screened annually through low-dose computed tomography.

Although cancer screening is part of a healthy approach to living, it can be difficult for individuals to ascertain which cancers to be screened for and when. The USPSTF and other relevant professional societies' recommendations are evidence-based guidelines that can help, but they are only one factor to consider when making decisions about cancer screening.

People have their own unique risks for developing each type of cancer. These risks are determined by genetic, molecular, cellular, and tissue makeup, as well as by lifetime exposures to the large number of factors that can increase the risk of developing cancer (see **Figure 4**, p. 15). As a result, each individual should consult with his or her physicians to develop a personalized cancer-screening plan that takes

into account evidence-based recommendations; the individual's own cancer risks, including family history; and the individual's tolerance of potential screening harms (see sidebar on **Cancer Screening**, p. 28). Importantly, the risk for different types of cancer can vary over time—for example, risk for most cancers increases with age—so it is important that individuals continually evaluate, and update if necessary, their personalized cancer-screening plans.

Some generally healthy individuals are at increased risk of certain cancers because they inherited a cancer-predisposing genetic mutation (see sidebar on **How Do I Know If I Am at High Risk for Developing an Inherited Cancer?**). However, inheriting a cancer-predisposing genetic mutation is a relatively rare occurrence. In fact, only about 5 percent of all new cases of cancer diagnosed in the United States each year are caused by such mutations (63). To date, not all potentially inheritable causes of cancer have been identified, but if an individual suspects that a relative has a cancer caused by one of the 17 known cancer-predisposing genetic mutations (see **Table 5**), he or she should consult a physician and consider genetic testing for verification.

As part of a healthy approach to living, persons who are at risk for developing an inherited cancer—both those who learn they carry a known cancer-predisposing genetic mutation and those who fulfill criteria for being at risk—should consult

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);
- many cases of a particular cancer, such as breast cancer, among those on the same side of the family;
- members diagnosed with cancers at younger ages than usual (such as colon cancer in a 20-year-old);
- one or more members who have more than one type of cancer (such as a female relative with both breast and ovarian cancer);
- one or more members with cancers in both of a pair of organs simultaneously (both eyes, both kidneys, or both breasts); and
- more than one childhood cancer in a set of siblings (such as sarcoma in both a brother and a sister).

Adapted from:
cancer.org/Cancer/CancerCauses/GeneticsandCancer/heredity-and-cancer.

TABLE 5 | **INHERITED CANCER RISK**

CANCER	SYNDROME	ASSOCIATED GENE
Leukemias and lymphomas	Ataxia telangiectasia	ATM
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
Colorectal cancer	Familial adenomatous polyposis (FAP)	APC
Melanoma	Familial atypical multiple mole–melanoma syndrome (FAMM)	CDKN2A
Retinal cancer	Familial retinoblastoma	RB1
Leukemia	Fanconi's anemia	FACC, FACA
Colorectal cancer	Hereditary nonpolyposis colorectal cancer/ Lynch syndrome	MLH1, MSH2, MSH6, PMS2
Pancreatic cancer	Hereditary pancreatitis/familial pancreatitis	PRSS1, SPINK1
Leukemias, breast, brain, and soft tissue cancers	Li-Fraumeni	TP53
Pancreatic cancers, pituitary adenomas, benign skin, and fat tumors	Multiple endocrine neoplasia 1	MEN1
Thyroid cancer, 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, kidneys	von Hippel-Lindau syndrome	VHL
Kidney cancer	Wilms' tumor	WT1
Skin cancer	Xeroderma pigmentosum	XPD, XPB, XPA

with their physicians to determine how this influences their personalized cancer prevention and screening plans. Some patients may be able to reduce their risk of developing cancer by modifying their behaviors. Others might need to increase their participation in screening or early detection programs or even consider taking a preventive medicine or having risk-reducing surgery (see **Tables 6** and **7**).

Beyond inherited cancers, a number of medical conditions place an individual at higher risk for certain types of cancer. For example, ulcerative colitis and Crohn disease increase an individual's risk for colorectal cancer sixfold, but they are relatively rare conditions (64). A far more prevalent medical condition that increases an individual's risk for developing cancer is type 2 diabetes, which raises the risk of developing liver, pancreatic, and endometrial cancers (65, 66). These factors are important considerations when developing a personalized cancer-prevention and -screening plan.

Type 2 diabetes

affects about 8% of the U.S. population (67).

TABLE 6 | FDA-APPROVED MEDICINES FOR CANCER RISK REDUCTION OR TREATMENT OF PRECANCEROUS CONDITIONS*

CANCER RISK REDUCTION

Condition	Generic Name	Trade Name	Formulation
Breast cancer	raloxifene	Evista	
Breast cancer	tamoxifen	Nolvadex	
Cervical, vulvar, vaginal, and anal cancers and dysplasia; genital warts	human papillomavirus quadrivalent (types 6, 11, 16, and 18)	Gardasil	
Cervical cancer and cervical dysplasia	human papillomavirus (types 16 and bivalent 18) vaccine	Cervarix	

TREATMENT OF PRECANCEROUS CONDITIONS

Condition	Generic Name	Trade Name	Formulation
Actinic keratosis	ingenol mebutate	Picato	
Actinic keratosis	fluorouracil	Adricil	
Actinic keratosis	diclofenac sodium	Solaraze	
Actinic keratosis	5-aminolevulinic acid + photodynamic therapy (PDT)		
Actinic keratosis	masoprocol/nordi-hydroguaiaretic acid	Actinex	
Bladder dysplasia	bacillus calmet guerin/BCG		
Bladder dysplasia	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.

TABLE 7 | SURGERIES FOR THE PREVENTION OF CANCER

TECHNIQUE	PREVENTS	REMOVES
Colectomy*	Colon Cancer	Part of large intestine
Hysterectomy*	Uterine Cancer	Uterus
Mastectomy	Breast Cancer	Breasts
Oophorectomy	Ovarian Cancer	Ovaries
Orchiectomy*	Testicular Cancer and Prostate Cancer	Testes
Salpingo-oophorectomy	Ovarian Cancer	Ovaries and fallopian tubes

*not commonly performed for the prevention of cancer

TRANSFORMING LIVES THROUGH RESEARCH

IN THIS SECTION YOU WILL LEARN:

- FROM AUG. 1, 2013, TO JULY 31, 2014, THE FDA APPROVED SIX NEW THERAPEUTICS FOR TREATING CERTAIN TYPES OF CANCER.
- RESEARCH IS BEING PERFORMED TO HELP CANCER SURVIVORS MEET THE NUMEROUS CHALLENGES THEY FACE.
- FIVE OF THE NEW ANTICANCER THERAPEUTICS ARE MOLECULARLY TARGETED, AND ONE OF THESE IS ALSO AN IMMUNOTHERAPEUTIC.
- CANCER GENOMICS RESEARCH IS A FOUNDATION FOR NOVEL CLINICAL TRIALS DESIGNED TO ACCELERATE THE PACE AT WHICH NEW THERAPEUTICS ARE APPROVED FOR PATIENT CARE.
- DURING THE SAME PERIOD, THE FDA AUTHORIZED NEW USES FOR FIVE PREVIOUSLY APPROVED ANTICANCER THERAPEUTICS, TWO IMAGING AGENTS, AND ONE SCREENING TEST.

Research has the power to transform and save lives.

Yesterday's discoveries are being actively translated into tomorrow's breakthroughs, thanks to the dedicated efforts of researchers from across the entire biomedical research community, as well as patients and their health care providers. As a result, our journey toward the conquest of cancer continues to advance at an ever-increasing pace.

Biomedical Research

The cycle of biomedical research is fed by observations with the potential to have an impact on the practice of medicine. These observations emanate from laboratory research, population research, clinical practice, and clinical research including clinical trials (see **Figure 8**, p. 33), and are made by investigators working across the spectrum of research, from basic to population science (see sidebar on **Who We Are**).

WHO WE ARE

Biomedical researchers are often categorized by the type of work they do, although some individuals will 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:

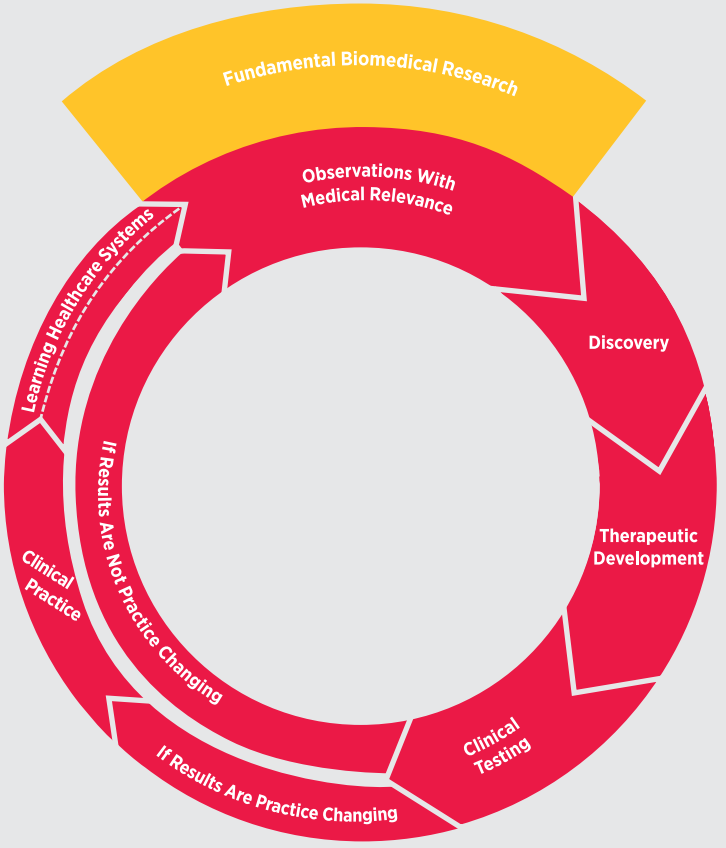
Basic researchers study animals, cells, molecules, or genes to gain new knowledge about cellular and molecular changes that occur naturally or during the development of a disease.

Population scientists, also known as epidemiologists, study the patterns, causes, and effects of health and disease conditions in defined populations. Epidemiological research is highly collaborative and can span the spectrum from basic to clinical research.

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).

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

FIGURE 8 | **THE BIOMEDICAL RESEARCH CYCLE**



Biomedical research begins with 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 sidebars on **Who We Are**, p. 32, and **Research Models**, p. 34). 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. 35). Before entering clinical testing, potential therapeutics are subjected to preclinical testing to identify any toxicities and help with 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. 38). If a therapeutic is safe and effective and is approved for use by the U.S. Food and Drug Administration (FDA), it will enter into clinical practice, where it can transform the lives of patients. Importantly, observations made during the routine use of a new therapeutic can feed back into the biomedical research cycle and further enhance the use of that therapeutic or the development of others like it. If, however, a therapeutic is not safe or effective and fails to gain FDA approval, the observations from the clinical testing can feed back into the biomedical research cycle to spur future research efforts. Because the cycle is iterative, it is constantly building on prior knowledge.

Ultimately, the observations lead to questions, or hypotheses, that are tested in experiments, the results of which add to or change current clinical practice, or feed back into the cycle for another iteration of testing. Importantly, because the cycle is iterative, it is constantly building on prior knowledge.

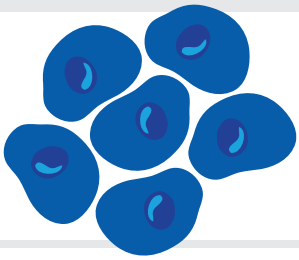
Figure 8 depicts the continuum of biomedical research. The cycle can be divided into several discrete stages of research, and a brief description of each follows.

Discovery

In the discovery phase of research, hypotheses generated from observations with medical relevance, are tested in experiments performed using models, ranging from single cells to whole animals, that mimic healthy and disease conditions (see sidebar on **Research Models**, p. 34). In clinical research, these models are derived from patients. Cancer research uses models that mimic specific aspects of cancer or types of cancer—for example, increased cell growth or pancreatic cancer, respectively.

RESEARCH MODELS

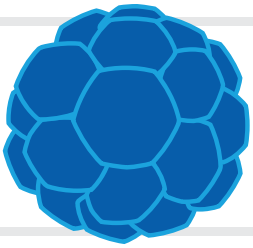
Researchers use a variety of models to mimic what happens in healthy and disease conditions. Below are some of the most common models used.



Cell lines are cells of different origins that can be grown continuously in the laboratory.

Primary cells are cells that are obtained directly from healthy or diseased tissues of either human or animal origin.

Tissues are pieces of or entire healthy or diseased tissues from humans or animals. They are obtained through biopsies or surgery.



Organoids are engineered 3-D structures generated from healthy or diseased components, which resemble an organ in cellular composition and organization.

Many different animal models are used in biomedical research. Mice are the most commonly used models, but zebrafish and dogs are emerging as very good models for certain types of cancer. Less frequently used animal models include rodents other than mice, cats, fruit flies, nematodes (worms), pigs, and primates.

Other models include yeast.

Therapeutic Development

The majority of research and therapeutic development performed today is "target based," meaning that it focuses on traits unique to a disease that were uncovered during the discovery research process (see sidebar on **Therapeutic Development**, p. 35). Once these targets are identified, they are then validated, meaning that the relationship of the trait to the disease state is confirmed, and then panels of potential therapeutics are tested to determine if they are capable of hitting and altering the target. A group of potential therapeutics that are capable of modifying the target, also known as "hits," are then further studied to identify the most promising, which is referred to as the lead therapeutic. Lead therapeutics then go through an optimization process that aims to enhance potency and other factors while reducing toxicity. During preclinical testing, a lead therapeutic is rigorously assessed in animal models to identify any potential toxicity and to further study potency prior to testing in humans.

THERAPEUTIC DEVELOPMENT

Target validation.
Potential therapeutic targets identified in discovery research are confirmed to play a 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.
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 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.

Clinical Trials

Before a medical product can be used routinely in patient care, it must be rigorously tested in clinical trials, which provide each patient with the best care available (see cancer survivor **Jack Whelan,** p. 36). As highlighted by **Carlos L. Arteaga, MD** (see p. 82), perhaps one of the most significant advances taking place in clinical care in recent years is the fact that clinical trials are no longer seen as a last option, but rather can be incorporated as part of regular care after discussions between physician and patient.

SURVIVING WALDENSTRÖM MACROGLOBULINEMIA THANKS TO RESEARCH AND CLINICAL TRIALS

I was diagnosed with Waldenström macroglobulinemia, a rare and incurable blood cancer, in 2007. After conventional treatments failed to improve my condition, I have been fortunate to have participated in five different clinical trials that have given me access to world-class care with novel cancer medicines that have allowed me to live a full and active life.

I learned recently that my disease has relapsed; however, I have faith that scientific advances will help me get through this challenge. In fact, as a result of such advances, the U.S. Food and Drug Administration (FDA) is currently reviewing a new targeted drug for the treatment of Waldenström, and others are under evaluation in clinical trials.

Shortly after my 58th birthday, I began to notice that my daily power walks from the train station to the office were becoming more difficult. My first thought was that I must be getting older, but I had also experienced a few nosebleeds and generally didn't feel as strong as usual, so I scheduled an annual physical with my primary-care physician.

The regular battery of tests ordered by the doctor revealed high levels of protein in my blood, so he referred me to a hematologist-oncologist at my local hospital. After more tests, which included a bone marrow biopsy, I was diagnosed with Waldenström macroglobulinemia, also known as lymphoplasmacytic lymphoma. It is a rare type of non-Hodgkin lymphoma; only about 1500 people are diagnosed with it each year in the United States.

Because Waldenström is so rare, my local hematologist had never treated anyone with the disease. I asked her where she would choose to be treated if she were in my position, and she said an academic medical center. I chose the Dana-Farber Cancer Institute in Boston, which has a program for patients with Waldenström. It has been one of my best decisions ever: My medical team there has been absolutely amazing.

Patients with Waldenström who are not experiencing symptoms are often not treated immediately. However, as my disease was already symptomatic, I began treatment right away. Because there are no FDA-approved treatments for Waldenström, my doctors borrowed from the approved treatment arsenal for other types of lymphomas and leukemias. I started with plasmapheresis, a blood-filtering process designed to lower levels of the protein IgM [immunoglobulin M] in my blood (the abnormally high blood levels of IgM cause many of the symptoms of Waldenström, including the nosebleeds I was experiencing), and weekly infusions of a therapy called rituximab (Rituxan).

Unfortunately, my disease did not respond to these treatments—my blood IgM levels remained high and my bone marrow was still overrun with cancer cells. After researching my options, I decided that rather than pursue further traditional chemotherapies, I wanted to try more targeted therapies, which seemed to be safer and cause fewer toxic side effects. The only way to do this was through clinical trials. Being cared for at Dana-Farber, by oncologists who focus on research and who treat Waldenström patients, gave me this opportunity.

I participated in four early-phase clinical trials. The first three had only modest effects on my disease. However, the drug that I received through the fourth trial, panobinostat, worked beautifully—my blood IgM levels came down dramatically, and although my blood chemistry biomarkers never reached normal levels, they were stable. In November 2012, after 18 months on the trial, I had to stop taking panobinostat because it became too toxic for my body. My blood pressure skyrocketed, and the headaches I had been experiencing became intolerable.

My disease remained stable for 10 months, even with no treatment, but at the end of March (2014), I discovered that my disease had relapsed. Since this time, I have begun yet another clinical trial, a combination targeted therapy of carfilzomib, rituximab, and dexamethasone; although still early, we're seeing an initial response that is very good.

My diagnosis led me to make some pretty compelling changes in my life. I retired from my work as an IT research analyst at an institutional investment firm and became involved in advocating for a different, more important, kind of research—cancer research.

I have confidence that the scientific advances made by cancer researchers will continue to increase the number of safer, more effective options for patients, including those with Waldenström. But unless more patients participate in clinical trials, these options might not become a reality for everyone. Given that my continued well-being owes so much to my participation in clinical trials, I have become a passionate advocate for them; it is vital that we educate everyone about their importance and dispel the myths and misconceptions surrounding them. They offer an unparalleled level of care.

JACK WHELAN
AGE 65
ANDOVER, MASSACHUSETTS

“I have confidence that the scientific advances made by cancer researchers will continue to increase the number of options for patients.”

Waldenström macroglobulinemia is a rare form of non-Hodgkin lymphoma.

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Clinical trials are used to evaluate the safety and efficacy of a potential medical product before it can be approved by the FDA and used more broadly as part of standard care. All clinical trials are reviewed and approved by the FDA and 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 general, they add an investigational intervention to the standard of patient care. The following discussion focuses on treatment trials, which are used to evaluate potential new anticancer therapeutics.

Until recently, treatment clinical trials have been typically done in three successive phases, each with an increasing number of patients (see sidebar on **Phases of Clinical Trials**). One of the many advances in clinical research has been the advent of new ways of conducting and regulating clinical trials, which can eliminate the need for large, long multiphase trials (see below).

Conventionally, many adult clinical trials are conducted after patients have received prior treatments, like surgery, radiation, or other therapeutics, which have already been tested in prior clinical trials. In some cases, a clinical trial may be designed to test a presurgery treatment, which is referred to as a neoadjuvant treatment. Recently, such a trial was the basis upon which the FDA approved a new use for a previously approved breast cancer therapeutic called pertuzumab (Perjeta) (see **New Path to Approving Breast Cancer Therapeutics**, p. 64).

PHASES OF CLINICAL TRIALS

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).

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 (see **Figure 8**, p. 33).

For more than a decade, the process of therapeutic development has been steadily moving toward the production of therapeutics that precisely target the molecules disrupted as a consequence of cancer-specific genetic mutations. Unfortunately, it is estimated to cost more than $1 billion and take more than a decade to develop a targeted therapeutic and bring it to market (68). Thus, numerous efforts have been made to streamline clinical research. Some of these efforts are aimed at matching the right drugs to the right patients, whereas others focus on reducing the number of patients that need to be enrolled in a particular trial. Yet others are designed to reduce the time needed for the trial to continue before a clear result can be achieved—for example, by using alternative or surrogate endpoints (see sidebar on **Alternative (Surrogate) Clinical Trial Endpoints**) and expedited review strategies (see sidebar on **FDA's Expedited Review Strategies**, p. 40).

ALTERNATIVE (SURROGATE) CLINICAL TRIAL ENDPOINTS

The best clinical trial endpoint for evaluating anticancer therapeutics is overall survival, which is defined as the percentage of patients still alive at a certain time point after they started treatment for a disease. However, determining overall survival may take too long and, in turn, delay access to potentially lifesaving medical products. Thus, the U.S. Food and Drug Administration (FDA) commonly uses the following surrogate endpoints or "direct measures of how a patient functions, feels, or survives" for approval of anticancer drugs.

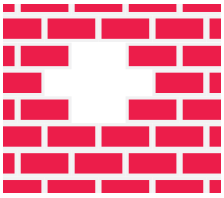
PFS	**Progression-free survival (PFS)** is the length of time patients survive without their disease getting worse.
DFS	**Disease-free survival (DFS)** is the length of time after treatment that a patient survives with no sign of disease.
pCR	**Pathologic complete response (pCR)** is the absence of any detectable residual invasive cancer in a surgical specimen after presurgery treatment.
ORR	**Overall response rate (ORR)** is the percentage of patients in a trial whose cancer shrinks and/or disappears after treatment.

FDA'S EXPEDITED REVIEW STRATEGIES

The 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 to verify that it provides clinical benefit following approval. Ponatinib (Iclusig) for the treatment of chronic myeloid leukemia (CML) was approved under this pathway in December 2012.

Fast track. This designation is given to drugs 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. Ipilimumab (Yervoy) for the treatment of metastatic melanoma was approved through fast track in March 2011.



Breakthrough therapy. A drug 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 November 2013, after receiving a breakthrough therapy designation is obinutuzumab (Gazyva) for the treatment of chronic lymphocytic leukemia (see p. 53).

Priority review. Drugs that have the potential to significantly improve safety or effectiveness may be granted priority review after all clinical trials are completed. This allows the drug to be assessed within six months as opposed to the standard 10 months. Radium Ra 223 dichloride (Xofigo) was granted priority review and approved for the treatment of prostate cancer that has spread to the bones in May 2013.

Two examples of clinical trials aimed at matching the correct therapy with the correct patient subset are BATTLE-2 and the I-SPY 2 TRIAL (I-SPY 2). In each of these unique clinical trials, a patient's tumor is examined for unique signatures called biomarkers. The biomarker signatures are used to simultaneously test and match multiple investigational therapies to individual patients, thus maximizing the number of patients likely to benefit. These trials have numerous efficiencies, but the major efficiency is enabling a phase III trial that is smaller than is traditionally needed because, in an adaptive trial, only patients most likely to respond are included in the study.

The I-SPY 2 TRIAL

graduated two drugs, neratinib and velipirib, to phase III trials for potential registration as new drugs, as of July 31, 2014.

One of the major advances provided by the use of genomics in clinical research is the ability to use novel clinical trial designs to assign the correct therapy to the correct patient earlier and to improve organ-based classifications of cancers by including a description of the underlying genomic alterations. Such trials can take the form of basket or umbrella trials (see **Figure 9**). Basket trials aim to test one drug or one particular genetic mutation across multiple organs. Umbrella trials seek to test a drug or drugs across multiple genetic mutations within a particular type of cancer. For example, I-SPY 2 and BATTLE-2 are umbrella trials in breast and lung cancer, respectively.

Two ambitious umbrella trials are just getting underway and are possible only because of advances in DNA sequencing technology. The first of these, the Lung-MAP study, is a phase II/III trial that aims to test for multiple types of mutations in hundreds of genes prior to assigning patients with squamous cell lung carcinoma to one of five investigational drugs, including an immunotherapy (see **Treatment With Immunotherapeutics**, p. 65). The NCI-MATCH trial is another phase II umbrella trial using advanced DNA sequencing technology to identify multiple types of mutations in hundreds of genes prior to assigning patients to one of numerous investigational therapeutics.

In addition, physician-scientists like **Nikhil Wagle, MD** (see p. 42), are using genomics to help understand why some individuals, referred to as rare responders, have exceptionally good responses to a treatment received as part of a clinical trial, whereas the majority of individuals do not gain benefit from the therapy.

Whole exome sequencing

refers to sequencing only the ~3% of the DNA that codes for proteins, rather than sequencing all DNA bases.

FIGURE 9 | **GENOMICALLY BASED 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) within lung cancer.

IMPACTING CLINICAL CARE THROUGH GENOMICS RESEARCH

There's been a revolution in cancer genomics and genomics research over the past decade, thanks to the plummeting cost of sequencing and the development of new technologies. As a result, we understand much more about the molecular underpinnings of cancer biology, and this is beginning to influence clinical decision making. Further developing this base of knowledge is really the key to better implementing precision medicine.

In recent years, there has been a shift in the treatment of cancer patients from less targeted, traditional therapies toward the use of molecularly targeted therapies. This approach to treatment is known as precision medicine. It is a direct result of genomic analyses in the research laboratory being used to inform molecularly targeted drug development. As our understanding of the molecular dependencies of tumors grows, so, too, will the number of molecularly targeted drugs.

We are now witnessing great advances as genomic analyses are increasingly being applied to the clinical research setting. For example, we are using genomics to understand the molecular features of a tumor that can influence treatment decisions, tell us about the likelihood of response or resistance to certain therapies, help with diagnosis, and give clues about prognosis.

Although genomic analysis doesn't help all patients, there is an increasing number of patients for whom it has impacted clinical decision making. For example, whole-exome sequencing of the tumor from one patient with advanced lung cancer revealed three potentially clinically relevant genetic alterations that hadn't been detected by standard testing. As a result of our analysis, the treating physician enrolled the patient in a clinical trial that stabilized his disease for many months, which was the best response he had had to date. When that trial ended, another clinical trial was identified from which he might benefit, based on our prior genomic analysis, and as a result, he continues to do well.

The use of genomics clinically has become increasingly important for understanding why there is diversity in the response of patients to anticancer therapies. We have always known that some patients respond to certain therapies and others do not, but in most cases we don't know why these differences occur. Over the past few years, we have seen that studying "exceptional responders"—rare patients with exquisite sensitivity or unexpected long durations of response to therapies—is a good way to shed light on this issue.

We have found that in several exceptional responders, we are able to identify the mutation, or combination of mutations, that makes these patient's tumors extraordinarily responsive to the treatments. The next step is to look for the same or similar mutations in other patients and enroll them in clinical trials to see if they, too, might respond well to the therapy. In fact, analysis of exceptional responders has seeded a number of so-called "basket" trials, in which patients are enrolled based primarily on the genetic alterations of their tumors as opposed to an anatomical basis or specific clinical features.

Genomic analysis is also key to understanding how tumors become resistant to molecularly targeted therapies. What we've learned is allowing us to begin to predict which patients will likely have a tumor that is resistant to a certain therapy and to identify combinations of therapies that will overcome resistance.

We are beginning to see genomic analysis move from the research setting to standard of care, but there are still challenges that must be overcome if this trend is to increase dramatically in the next few years. The key challenge is assembling enough data to support meaningful analysis. Frankly, we need data from sequencing of hundreds of thousands of tumors, submitted to large, centralized, shared databases. Moreover, the data have to be interpreted and annotated, and then communicated so that both patients and physicians can understand how to use this information in making the best treatment decisions.

The ultimate goal is for genomic analysis to be part of the routine battery of pathological and diagnostic tests run on tumor tissue from all cancer patients in order to determine the optimal care for each individual.

NIKHIL WAGLE, MD

INSTRUCTOR IN MEDICINE AT
THE DANA-FARBER CANCER INSTITUTE, BOSTON, AND
ASSOCIATE MEMBER OF THE BROAD INSTITUTE,
CAMBRIDGE, MASSACHUSETTS

"The ultimate goal is for genomic analysis to be part of the routine... in order to determine the optimal care for each individual."

Photo courtesy of Dana-Farber Cancer Institute

Genomics is also being used to identify new patients who might benefit from previously approved molecularly targeted therapeutics. This is now possible because researchers are increasingly discovering that different types of cancer are driven by similar genetic abnormalities. Thus, molecularly targeted therapeutics that were first developed and FDA approved for the treatment of one type of cancer can now be repurposed as treatments for patients with a different type of cancer driven by similar genetic abnormalities. Approaches like these have the potential to benefit many patients.

For example, after genomics research established that about 5 percent of cases of the most common form of lung cancer, non–small cell lung cancer (NSCLC), are driven by genetic mutations that lead to altered expression and activity of the signaling protein ALK, researchers set out to develop ALK-targeted therapeutics. In August 2011, the FDA approved one such therapeutic, crizotinib (Xalkori), for the treatment of patients with ALK-positive NSCLC. After it was found that between 10 and 15 percent of childhood anaplastic large cell lymphomas (ALCLs) are also driven by ALK (69), researchers began testing crizotinib as a treatment for pediatric patients with ALCL. Early results from these trials have been very promising (70), with several patients, such as **Zachery (Zach) Witt** (see p. 46), having complete responses.

As discussed earlier, these advances in clinical research are possible only because of the ability to perform high-density genetic analysis of the tumors from patients in a given study. In November 2013, the FDA cleared the first high-throughput (next-generation) genomic sequencer, the Illumina MiSeqDx instrument and companion Universal Kit reagents, for broad clinical use. Together, this machine and these reagents are capable of reading a patient's entire genome and assisting in the identification of multiple types of genetic mutations.

Because of the sheer amount of data generated by genomic studies, advanced computation and "big data" science are needed to help make sense of the data, as well as define new relationships between the data elements (see **Figure 10**, p. 45). The need to understand big data is great, not only in clinical research but also in all of biomedical research.

Big data

refers to data sets so large and complex that they are difficult to analyze using traditional data processing methods. For example, predicting the weather is a big data problem.

Without question, genomics and the use of big data are revolutionizing clinical research, and it is anticipated that the use of genomics will soon become part of the standard of care in oncology (see **What Progress Does the Future Hold?**, p. 80).

Progress Against Cancer Across the Clinical Care Continuum

The tools that we use routinely to prevent, detect, diagnose, and treat cancer were developed as a result of extraordinary medical, scientific, and technical advances fueled by cancer research. In fact, it takes many years of dedicated work by thousands of individuals across the biomedical research community to bring a new medical product from concept to FDA approval.

In the 12 months leading up to July 31, 2014, the FDA approved six new anticancer therapeutics. During this time, the FDA also approved a new use for a previously approved test for detecting the cancer-causing pathogen HPV; new uses for two imaging agents; and new uses for five previously approved anticancer therapeutics, including a nanodrug form of paclitaxel (Abraxane), a traditional chemotherapy used to treat a number of cancer types.

Nanodrugs:

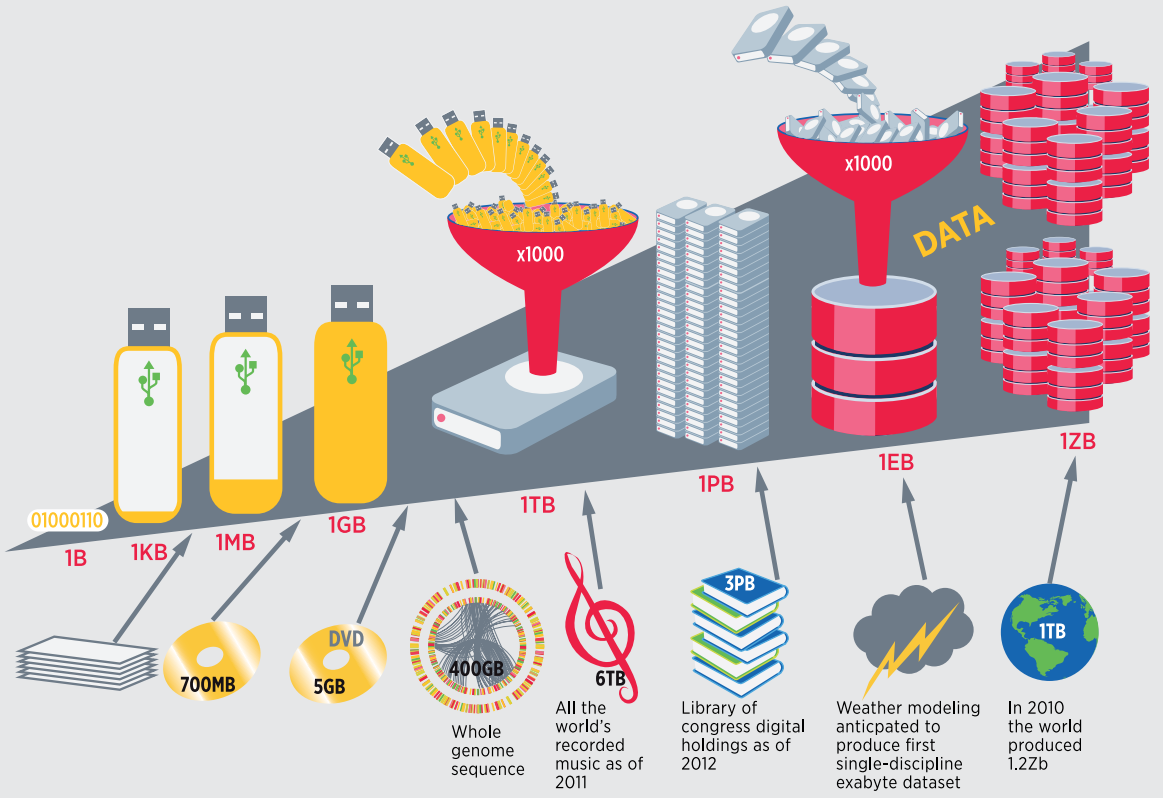
are 20,000 times smaller than the smallest width of a human hair.

comprise an anticancer agent and a nanosized carrier that selectively delivers the drug to the cancer and protects the drug from being destroyed by the body.

increase efficacy of the anticancer agent while reducing toxic side effects.

FIGURE 10 | **HOW BIG IS BIG?**

Data of any kind are measured in bytes. A byte is 8 binary digits (the 01011010 above) and is recognized by a computer as a single character. A thousand bytes make up a kilobyte (kB); the average Word document (stack of paper) 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 Global Institute (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 6000 1-GB thumb drives to store all of this data (73). As of April 25, 2012, the Library of Congress' digital holdings collection contained 3 petabytes (PB; bookcase) of data, which totals 3000 terabytes or 3 million 1-GB thumb drives (74). Researchers at the Lawrence Berkeley National Laboratory forecast 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 (71). It is estimated that in 2010, the world collectively created more than 1.2 zetabytes (ZB; globe) of data (72). Big datasets are unique in that they are too large to be stored and analyzed using traditional methods. The complexity of cancer and its treatment is creating big datasets, and the field and the patients it serves will benefit greatly from research into how to optimize systems for storing, accessing, and analyzing big data.



OVERCOMING ANAPLASTIC LARGE CELL LYMPHOMA THANKS TO THE LUNG CANCER DRUG CRIZOTINIB

A message from John and Pam Witt, Zach's parents:

Our son Zach was diagnosed with anaplastic large cell lymphoma when he was just 5 years old. He relapsed before he had completed his initial treatment—a year of standard chemotherapy—and seemed to be getting sicker every day. But then he received a new kind of drug, one that was targeted to his cancer, and within a few days we saw a dramatic change: We got our boy back. He is now living life like any normal 9-year-old—going to school, playing baseball, and riding his bicycle—and there is no doubt in our minds that without cancer research Zach would not be here today.

Right up to the time of Zach's diagnosis in September 2010, we had no clue that anything was wrong. It all happened very suddenly. One day John lifted Zach up and Zach complained that the "bump" under his arm hurt. We looked and saw a pretty good-sized lump in his armpit. The next day, we took him to the pediatrician, who sent Zach for blood tests right away. That evening, we went to the ER [emergency room] and were relieved when the test results came back normal.

However, a few days later our pediatrician called and said he was still concerned and wanted us to take Zach to an oncologist for further tests. We took him to Children's Hospital of Philadelphia (CHOP), and within a few days we received the diagnosis. It was a huge shock to us. We could barely believe it was happening.

Almost immediately, Zach started the standard treatment for children with anaplastic large cell lymphoma, which was chemotherapy for a year. The chemotherapy made him really sick, and he was in and out of CHOP for months with fevers and low blood cell counts. But his cancer seemed to be responding.

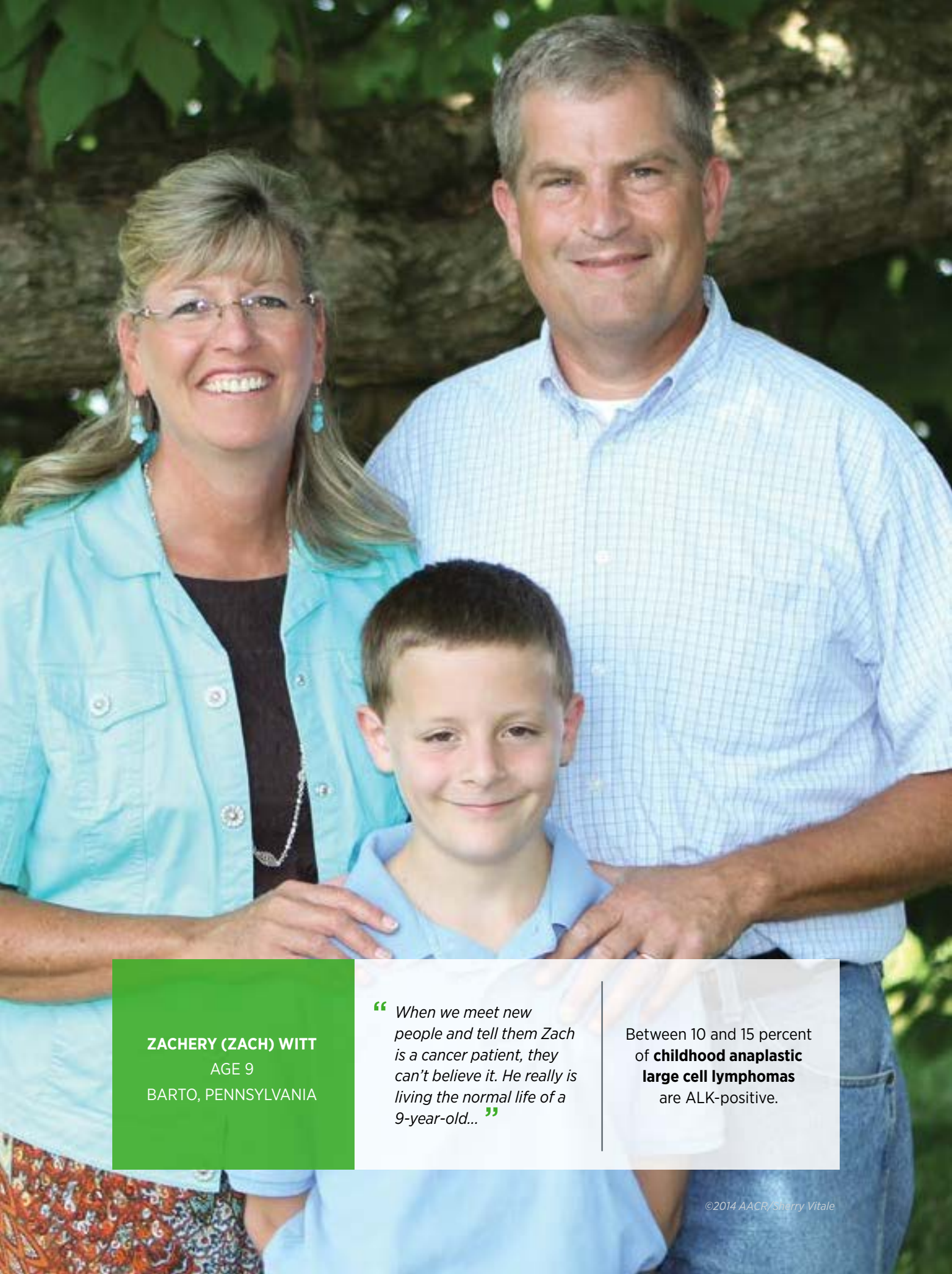
Then, even though he was still on treatment, Zach started getting flu-like symptoms and fevers again. On a day that seemed to match our feelings exactly—it was a cloudy, dreary March day—Zach's relapse was confirmed.

We had a meeting with the doctors at CHOP to discuss Zach's treatment options. One option was more aggressive chemotherapy. We couldn't imagine how that was possible having seen how sick the initial chemotherapy had made Zach. The other option was a clinical trial. The doctors told us that a genetic test they had run on a cancerous lymph node removed during Zach's initial diagnosis had shown that his cancer was ALK-positive. The clinical trial they talked about was testing a drug that targeted ALK (crizotinib, which was FDA-approved in August 2011 to treat certain patients with lung cancer), and they were looking to enroll children with ALK-positive cancers in the trial.

Pam was fearful of enrolling Zach in the clinical trial, but John could hear the optimism in the doctors' voices as they talked about the trial. Pam was finally won over after she asked one of the doctors, "If this were your child, what would you do?" and he immediately replied that he would enroll his child in the study.

It took a few days before Zach could begin treatment with crizotinib, and at this point he was so tired he couldn't get out of bed to go to the playroom in the hospital. Just three days after starting crizotinib, in April 2011, he ran down the hallway to the playroom. We couldn't believe it was the same kid.

Zach still takes crizotinib twice a day and has checkups once a month. But the tests and scans show no sign of disease, and he is back to being the high-octane boy he was before his diagnosis. When we meet new people and tell them Zach is a cancer patient, they can't believe it. He really is living the normal life of a 9-year-old, and that is why we tell his story.



ZACHERY (ZACH) WITT
AGE 9
BARTO, PENNSYLVANIA

"When we meet new people and tell them Zach is a cancer patient, they can't believe it. He really is living the normal life of a 9-year-old..."

Between 10 and 15 percent of **childhood anaplastic large cell lymphomas** are ALK-positive.

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The nanodrug form of paclitaxel was approved by the FDA for the treatment of metastatic pancreatic cancer in September 2013. This FDA approval followed earlier approvals of this nanotherapeutic for the treatment of patients with breast or lung cancer. It was the result of clinical trials showing that the nanodrug form of paclitaxel transformed the lives of many patients, like Dr. Charles Haerter (who was featured in the *AACR Cancer Progress Report 2013* (5)), diagnosed with one of the most deadly forms of cancer (75).

6%

of pancreatic cancer patients survive five years after diagnosis (1).

In the quest to prevent and cure cancer, these new tools are used alongside those already in the clinician's armamentarium. Thus, most patients are treated with a combination of surgery, radiotherapy, chemotherapy, and immunotherapy (see **Appendix Tables 1 and 2**, p. 106). In June 2014, the FDA approved a new use for the radioactive diagnostic imaging agent technetium Tc 99m tilmanocept (Lymphoseek) that will benefit some patients with head and neck cancer who are undergoing surgery. The agent can now be used to help surgeons find the sentinel lymph node(s) in patients with head and neck cancer, limiting the need for further surgery in patients with cancer-free lymph nodes and potentially improving postsurgical treatment decisions.

The following discussion focuses on recent FDA approvals that are transforming lives by having an impact on clinical care across the spectrum of cancer prevention, detection, diagnosis, treatment, and continuing care. It also highlights some advances across the continuum of clinical care that are showing near-term promise.

Cancer Prevention, Detection, and Diagnosis

The most effective ways to reduce the burden of cancer are to prevent cancer from developing in the first place and, if cancer does develop, to detect it as early as possible. As research provides new insights into the factors that increase a person's risk of developing cancer (see **Figure 5**, p. 15) and the timing, sequence, and frequency of the genetic, molecular, and cellular changes that drive cancer initiation and development, we have been able to develop new ways to prevent cancer onset or to detect a cancer and intervene earlier in its progression. In some cases, strategies to detect a cancer also provide key information for diagnosis.

HPV Holds New Keys to Cancer Prevention

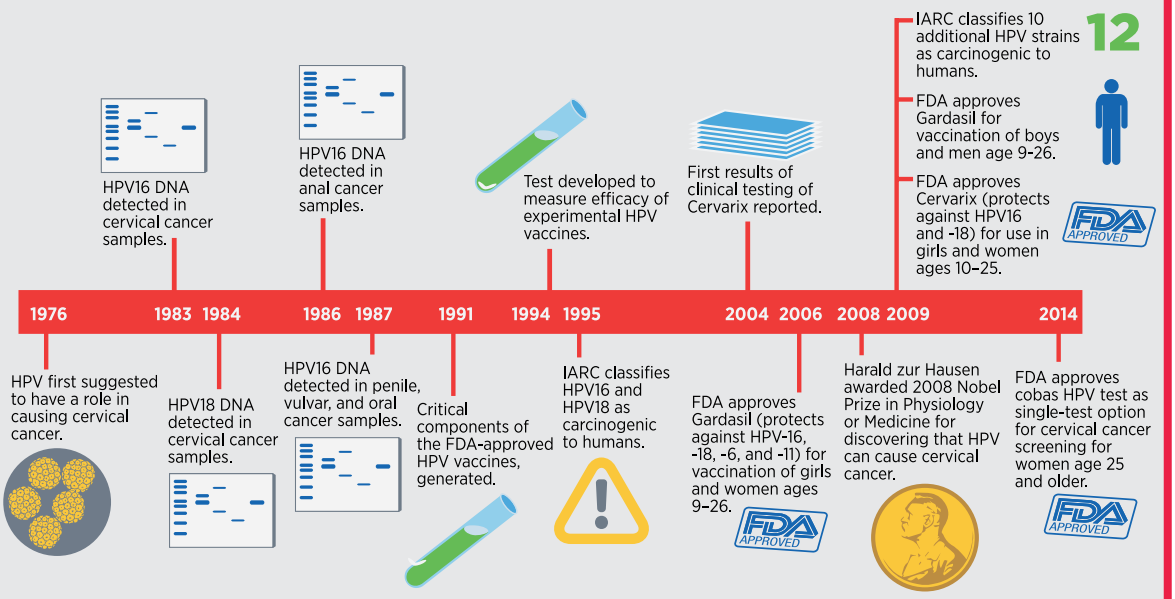
Almost all cases of cervical cancer are attributable to persistent cervical infection with certain strains of HPV (42) (see **Figure 7**, see p. 23). Over time, this knowledge enabled two approaches for cervical cancer prevention and early detection: the development of vaccines that prevent infection with some cancer-causing strains of HPV and the development of a clinical test for detecting cancer-causing HPV strains (see **Figure 11**, p. 49). Several recent advances could accelerate the pace of progress against cervical cancer, which affects more than 500,000 women each year worldwide (6) (see sidebar on **Recent Advances in Cervical Cancer Prevention and Early Detection**, p. 49). Given that a substantial proportion of vulvar, vaginal, penile, and anal cancers, as well as some head and neck cancers—like the stage IV throat cancer that **Robert (Bob) Margolis** (see p. 50) was diagnosed with in 2007—are also caused by HPV, these advances may have broader implications for reducing the global burden of cancer.

The two HPV vaccines currently approved by the FDA protect against infection with just two cancer-causing strains of HPV, HPV16 and HPV18. Although these are the two most common cervical cancer-causing HPV strains (44), researchers have been working to develop vaccines that protect against a greater number of the cancer-causing HPV strains. Recent results indicate that one vaccine that protects against seven cancer-causing HPV strains (HPV16, -18, -31, -33, -45, -52, and -58) can prevent precancerous cervical abnormalities caused by these strains (76).

The proportion of cervical cancer cases caused by individual HPV strains varies in different regions of the world and among different segments of a given population. For example, HPV16 and HPV18 account for more cases in Europe, North America, and Australia compared with Africa, Asia, and South/Central America (79), and for more cases among non-Hispanic white women in the United States compared with black and Hispanic women (80). Thus, the HPV vaccine that protects against nine cancer-causing HPV strains may particularly benefit women from racial and ethnic minorities and those living in less developed nations. It may also reduce the burden of other HPV-related cancers, which are frequently attributable to cancer-causing strains other than HPV16 and HPV18 (44).

In the United States, it is recommended that individuals receive three doses of either of the FDA-approved HPV vaccines to best ensure that they are protected against infection with HPV16 and HPV18. However, recent research has shown that two doses of vaccine can generate HPV16- and HPV18-targeted immune responses comparable to those generated by three doses (77, 78). On the basis of these results, the European Commission decided to approve the marketing of a two-dose Gardasil schedule in April 2014 (81). If long-term studies confirm that two vaccine doses provide protection against cervical cancer, it could mean that individuals who failed to complete the three-dose

FIGURE 11 | **UNCOVERING HPV'S ROLE IN CANCER**

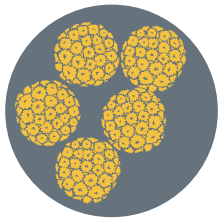


Human papillomavirus (HPV) was first suggested to have an important role in causing cervical cancer in 1976. During the ensuing years, researchers confirmed this hypothesis and identified the cancer-causing strains of HPV. They also found that certain strains of HPV cause many cases of anal, penile, vaginal, and vulvar cancers (see **Figure 7**, p. 23). Thirty years after the first suggestion of a cancer-causing role for HPV, the dedicated efforts of many basic and clinical researchers across the biomedical research enterprise culminated in approval by the U.S. Food and Drug Administration (FDA) of a vaccine that prevents infection with the two most common cervical cancer–causing HPV strains, HPV16 and HPV18, after the vaccine was shown to prevent precancerous cervical abnormalities caused by these strains. Since then, the FDA has approved a second HPV vaccine and the use of an HPV test called the cobas HPV test as a stand-alone option for cervical cancer screening for women age 25 and older. Research efforts are now focusing on developing vaccines that target more of the cancer-causing HPV strains and implementing effective strategies to increase vaccine usage.

RECENT ADVANCES IN CERVICAL CANCER PREVENTION AND EARLY DETECTION

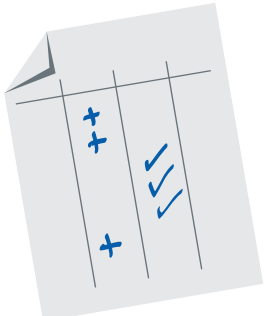
A new HPV vaccine designed to protect against seven cancer-causing HPV strains is highly effective at preventing precancerous cervical abnormalities induced by these seven HPV strains (76). Currently approved vaccines cover two of the most common cancer-causing strains.

9



Current practice recommends three doses of either HPV vaccine for complete protection; recent studies demonstrate that two may be just as effective as three (77, 78).

The U.S. Food and Drug Administration approved a test to detect HPV for use as a single-method tool to screen women at high risk for cervical cancer.



ROBERT (BOB) MARGOLIS
AGE 62
MACUNGIE, PENNSYLVANIA

"HPV-caused head and neck cancer is incredibly common, and the need to increase awareness about this is critical, especially among men ages 40–65."

Approximately 60% of head and neck cancers are caused by **HPV infection.**

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THREE-TIME CANCER SURVIVOR AND ADVOCATE FOR HPV AWARENESS AND VACCINATION

I am living proof that cancer is not a death sentence.

I survived three bouts with cancer: a diagnosis and recurrence of non-Hodgkin lymphoma and a diagnosis of stage IV HPV–related head and neck cancer. I believe I survived for a reason, and I am committed to educating others about the increasing number of head and neck cancer cases in the United States, an unfortunate circumstance in that this type of cancer can often be caused by infection with a sexually transmitted virus, the humanpapilloma virus (HPV). Fortunately, HPV infection can now be prevented by vaccination with either Gardasil or Cervarix.

As a sports writer covering NASCAR, I was always tired toward the end of the season after being on the road for 30-plus weekends. But in the fall of 2006, the tiredness was much worse than normal. Then, during one race weekend, I noticed a lump in my groin about the size of a golf ball. I was scared.

I saw my family doctor when I got home, and he took one look at the lump, which was now the size of a baseball, and told me to go to the hospital. There, after a CT scan of my entire body, the ER [emergency room] doctor came in and said, "It seems you may have something going on and it is possibly cancer."

The next day I saw an oncologist, and he told me that he believed I had diffuse large B cell lymphoma, a common type of non-Hodgkin lymphoma, but that surgery and a proper biopsy would confirm his diagnosis. This would have to wait, as I had plans to get married. So, on December 22, I got married in the Little White Chapel on the Strip in Las Vegas; the day after Christmas, I had surgery to remove the enlarged lymph node in my groin.

Next up were six rounds of chemotherapy. It was tough, but I went about my business covering NASCAR. I would have chemo on Tuesday, rest on Wednesday, and then fly to a race on Thursday. This schedule worked well until the fourth round of chemo. By then, I felt as though I were walking around in a lead suit at the race track. I was on pain meds, and my oncologist prescribed a drug called Marinol, which is a synthetic marijuana. But it didn't work, so I turned to medical marijuana, as it was the only thing that made my nausea and feeling of malaise any better.

During my chemo treatments, I had a lump on my neck that would shrink and come back again after each round. PET [positron emission tomography] scans following my final round of chemo still showed hot spots in my neck. My local oncologist assured me the lump would eventually go away with more chemo, but I wanted a second opinion. I went to see an oncologist at the Hospital of the University of Pennsylvania, who said, "You don't have non-Hodgkin lymphoma anymore; you have something else and you need to see Dr. Greg Weinstein at the Hospital of the University of Pennsylvania."

I saw Dr. Weinstein, an otorhinolaryngologist [ear, nose, and throat (ENT) specialist] the very next day. After two needle biopsies, he told me I had stage IV head and neck cancer caused by HPV. It was overwhelming. How could I still have cancer? I started crying, and as I got up to get a box of tissues, Dr. Weinstein stood up and hugged me. As he did, he said, "Don't worry, I'll make you better."

He was true to his word, but the treatment was tough. It consisted of a number of surgeries, including one that was done by the Da Vinci device, which is a robot, and very cool. I learned that my transoral robotic surgery (TORS) for oral cancer was part of a new procedure being pioneered by Dr. Weinstein.

After all my surgeries came more chemotherapy. Then came the radiation, and it was brutal. Monday through Friday, for six weeks, I was strapped to a table for 20 minutes of focused radiotherapy. The only thing that got me through my treatments was listening to one of my favorite Pink Floyd albums, "The Division Bell."

In March 2008, Dr. Weinstein declared me free of head and neck cancer, but it was about a year after that before I really felt better.

Having two cancers in one year was very difficult, and I would not have been successful in my battle without my wife and three daughters, who tirelessly helped me through the whole experience. They and others like them are the unsung heroes.

Unfortunately, in 2013, I had a recurrence of my non-Hodgkin lymphoma. Treatment of a relapsed disease was extremely different. It was far more difficult. Following four rounds of in-hospital chemo, I was admitted to the stem cell transplant program at the Hospital of the University of Pennsylvania, where I was treated by Dr. Jakob Svoboda. I was discharged from the active portion of the program in January 2014, although my scans and blood are still being monitored.

HPV-caused head and neck cancer is incredibly common, and the need to increase awareness about this is critical, especially among men ages 40–65. It can be difficult to discuss getting a sexually transmitted cancer, but it is time to talk about it. I have started a nonprofit organization called "High Performance Voices" to educate Americans about the pandemic of head and neck cancers and about how to talk to their doctor when they have that persistent sore throat or blister in their mouth. My nonprofit is also dedicated to educating young adults and parents about the HPV vaccines. We can prevent a generation of young Americans from having to go through the same experience I did.

course would benefit from the vaccine doses they received. Moreover, a two-dose vaccine schedule could potentially reduce costs and increase compliance, which would lead to broader protection of the population.

Testing for HPV, together with the standard Pap test, was first recommended as an alternative to the Pap test alone for cervical cancer screening 10 years ago (82). It was recently reported that an HPV test called the cobas HPV test, which detects all currently identified carcinogenic HPV strains, identified women at high risk for cervical cancer more effectively than the Pap test alone (83). As a result, the FDA approved the use of the cobas HPV test as a stand-alone option for cervical cancer screening for women age 25 and older in April 2014. This provides women with a less burdensome screening option and could potentially reduce health care costs.

High-risk, High-reward Prevention

The hormone estrogen fuels the growth and survival of about 70 percent of breast cancers. It does this by attaching to specific proteins called hormone receptors in and on the breast cancer cells. This knowledge led to the development of antiestrogen therapeutics more than three decades ago, and these medicines are the mainstay of treatment for patients diagnosed with hormone receptor–positive breast cancer.

Two antiestrogen therapeutics, tamoxifen (Nolvadex) and raloxifene (Evista), are approved by the FDA for the prevention of breast cancer in women at high risk for developing the disease. However, their use in this setting is not widespread, in part, because tamoxifen increases the risk for endometrial cancer, and both therapeutics may increase risk for blood clots and stroke.

In December 2013, results of a large-scale clinical trial showed that another antiestrogen therapeutic, anastrozole (Arimidex), more than halved breast cancer development among postmenopausal women at high risk for developing the disease, with very few side effects (84). Thus, anastrozole may, in the future, provide a new cancer prevention option for women at high risk for breast cancer, such as those at high risk for inherited forms of the disease (see sidebar on **How Do I Know If I Am at High Risk for Developing an Inherited Cancer?**, p. 30).

A Clearer Picture of Breast Cancer

Most women who receive a breast cancer diagnosis after a mammogram are referred for further testing to assess more precisely the size of the breast tumor and to determine whether the cancer has invaded local tissue or spread to other parts of the body. The results of these tests are important for providing the patient with an accurate diagnosis, which is crucial for deciding on the best course of treatment.

For some women, one of these follow-up tests is magnetic resonance imaging (MRI) of the breasts to establish the extent of the tumor within the breasts. MRI of the breasts can also be used to evaluate abnormalities seen by mammogram that were insufficiently clear for physicians to determine whether the patient has breast cancer or how large the tumor is.

In some cases, patients undergoing an MRI of the breasts are injected with a liquid called a contrast agent to help visualize abnormalities more clearly. In June 2014, the FDA approved a new contrast agent to use with MRI to assess the presence and extent of cancer within the breasts. This decision was made after the results of two large clinical trials showed that the new contrast agent, gadobutrol (Gadavist), significantly improved the ability of MRI to clearly visualize cancer in the breast.

Gadobutrol

was previously approved by the FDA for MRI of the central nervous system.

Treatment With Molecularly Targeted Therapeutics

Research is continually expanding our understanding of cancer biology. This knowledge is allowing us to treat cancer by targeting specific molecules involved in different stages of the cancer process. As a result, the standard of cancer care is changing from a one-size-fits-all approach to one in which the molecular makeup of the patient and his or her tumor dictates the best therapeutic strategy. This approach, variously called personalized cancer medicine, molecularly based medicine, precision medicine, or tailored therapy, is already transforming lives and will undoubtedly benefit many more patients in the future.

As a result of the greater precision of molecularly targeted therapeutics, they are more effective and tend to be less toxic than the treatments that have been the mainstay of patient care for decades. Thus, these new medicines are not only saving the lives of countless cancer patients but also improving their quality of life.

Molecularly Targeting Blood Cancers

Cancers that begin in blood-forming tissues, such as the bone marrow, or in cells of the immune system are called hematologic cancers or blood cancers. Three very recent FDA decisions have provided new treatment options for some patients with two types of hematologic cancer, chronic lymphocytic leukemia (CLL) and mantle cell lymphoma (MCL) (see sidebar on **Recent Advances Against Blood Cancers**, p. 53).

CLL is the most common type of leukemia diagnosed among U.S. adults age 20 or older, with 15,720 new cases projected to be diagnosed in 2014 (1). In the majority of cases, CLL arises in immune cells called B cells, or B lymphocytes, that have a protein called CD20 on their surface.

Given that CD20 is found only on B cells, both normal and CLL B cells, therapeutic antibodies that target CD20 were developed for the treatment of CLL. Two such therapeutic antibodies, ofatumumab (Arzerra) and rituximab (Rituxan), were approved by the FDA in October 2009 and February 2010, respectively. Although these two agents, when used in combination with traditional chemotherapies, significantly increase survival for many patients (85), a substantial number of patients have disease that does not respond to initial treatment or eventually becomes resistant to it (85, 86). As a result, researchers began working to develop more effective CD20-targeted therapeutic antibodies.

After attaching to CD20 on the surface of CLL cells, one of the ways in which rituximab and ofatumumab exert antileukemic effects is by flagging the CLL cells for destruction by immune cells. As a result, these agents can be considered molecularly targeted therapeutics and immunotherapeutics (see sidebar on **How Immunotherapeutics Work**, p. 65).

After basic immunology research uncovered a detailed molecular understanding of how rituximab attracts immune cells and instructs them to destroy the cells to which it is attached (87), bioengineers were able to create a new generation of CD20-targeted antibodies with enhanced ability to recruit immune cells and direct them to attack cancer cells (86).

One of the new generation of CD20-targeted antibodies, obinutuzumab (Gazyva), was approved by the FDA for the treatment of CLL in November 2013. This decision was made after early results from a large clinical trial showed that most patients with CLL lived significantly longer without their disease worsening when obinutuzmab was added to their traditional chemotherapy treatment, chlorambucil (88). Subsequent results from this clinical trial have shown that the addition of obinutuzumab to chlorambucil also provided an overall survival advantage compared with chlorambucil alone (89).

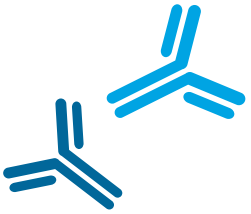
The FDA approval of obinutuzumab for the treatment of CLL was not only an important decision for patients with CLL, like **David Rampe** (see p. 54), but it was also a groundbreaking moment for regulatory science. This is because the use of obinutuzumab for the treatment of CLL was the first time a therapeutic was approved by the FDA after having been designated a "breakthrough therapy" (see sidebar on **FDA's Expedited Review Strategies,** p. 40).

Therapeutic antibodies

are proteins that have a therapeutic effect when attached to a specific molecule in the body. They are effective in the treatment of numerous cancer types and function in several different ways.

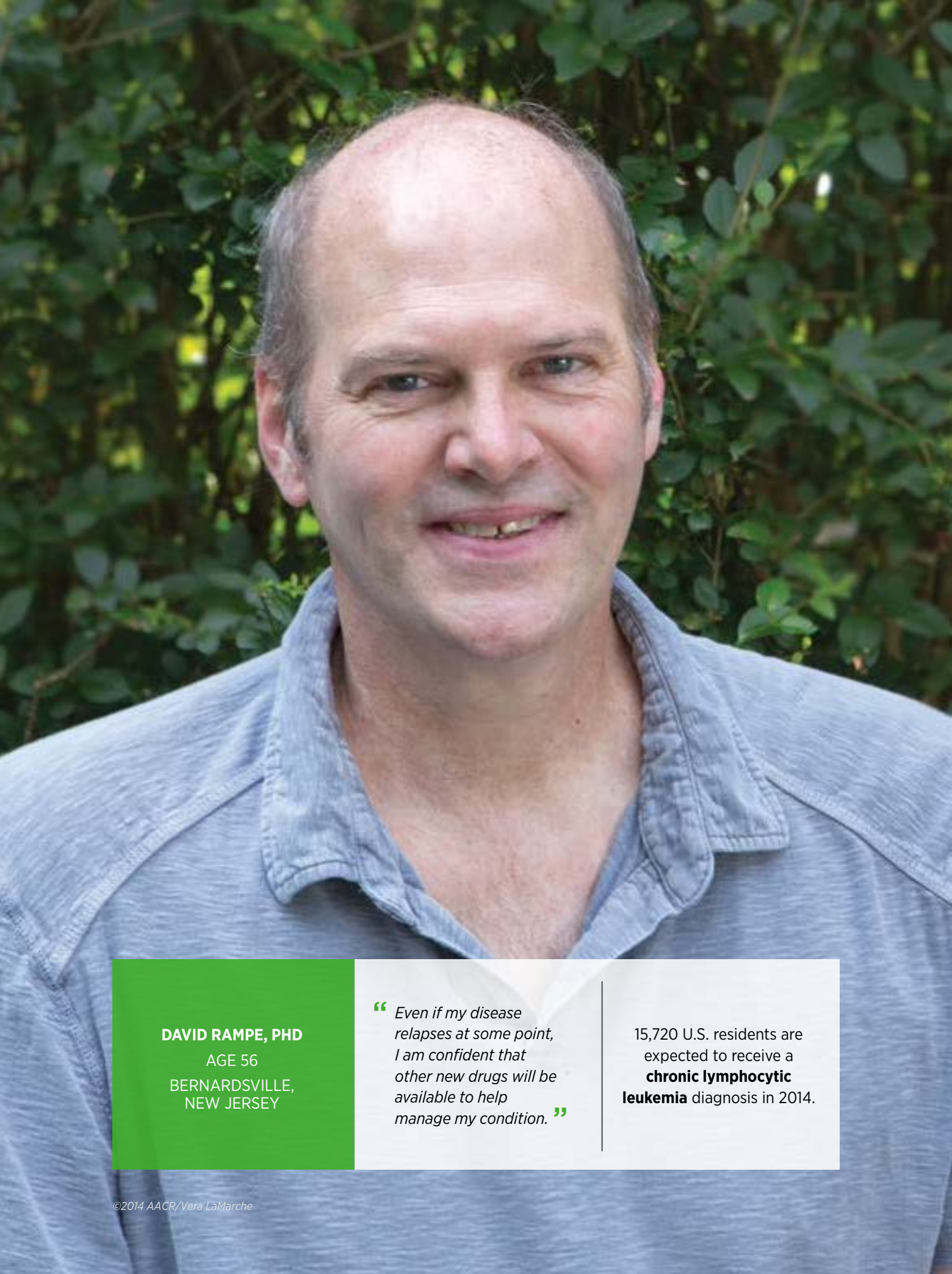
RECENT ADVANCES AGAINST BLOOD CANCERS

Obinutuzumab (Gazyva) is a molecularly targeted therapeutic and an immunotherapeutic that was approved by the FDA for the treatment of chronic lymphocytic leukemia (CLL) in November 2013.



Ibrutinib (Imbruvica) is a molecularly targeted therapeutic that was approved by the FDA for the treatment of mantle cell lymphoma in November 2013 and CLL in February 2014.

Idelalisib (Zydelig) is a molecularly targeted therapeutic that was approved by the FDA for the treatment of CLL, follicular B-cell non-Hodgkin lymphoma, and small lymphocytic lymphoma in July 2014.



DAVID RAMPE, PHD

AGE 56

BERNARDSVILLE, NEW JERSEY

"Even if my disease relapses at some point, I am confident that other new drugs will be available to help manage my condition."

15,720 U.S. residents are expected to receive a **chronic lymphocytic leukemia** diagnosis in 2014.

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LIVING WITH CHRONIC LYMPHOCYTIC LEUKEMIA SINCE 2006

I was diagnosed with chronic lymphocytic leukemia (CLL) in 2006. CLL usually progresses slowly, so there was a period of "watch and wait" before I needed treatment. In late 2013, I started treatment with a drug that had just been approved by the U.S. Food and Drug Administration (FDA), and now I am in remission and I feel fine. Even if my disease relapses at some point, I am confident that other new drugs will be available to help manage my condition.

I was 48 when I was diagnosed, which is young for CLL. A routine physical examination showed high white blood cell counts, specifically the lymphocytes, which we thought resulted from a case of bronchitis. But the same thing showed up the next year, and my family doctor consulted a hematologist, who said, "That could be CLL." And so it was.

I didn't have any symptoms except for the elevated white blood cell counts, so we did "watch and wait" for 7.5 years. I would visit my hematologist-oncologist every three months for checkups and blood tests. During 2013, however, I got progressively more anemic as my blood cell counts dropped, and so did my platelet numbers. That's called thrombocytopenia, and it meant that the CLL was impacting my bone marrow. I also started to get some swelling in the lymph nodes around my jaw and some swelling in my spleen. I was getting very tired—just going up a couple of flights of stairs left me out of breath. In December, the anemia and the thrombocytopenia were bad enough that it was time to pull the trigger and start some form of treatment.

The standard treatment for CLL is a chemotherapy regimen called FCR for the drugs involved, fludarabine, cyclophosphamide, and rituximab. It works well, but it can cause damage to the bone marrow and other problems down the line. So I wanted something that was new and more targeted toward the cancer itself, and something that would be a little bit gentler on the rest of my body.

My hematologist and I decided to go with obinutuzumab, a monoclonal antibody that had just been approved by the FDA under the brand name Gazyva. It works by attaching itself to certain proteins on the cancer cells and killing them; it also helps the body's immune system go after the cancer cells.

I had eight infusions over six months. I started just before Christmas 2013 and finished in May 2014. There were a few side effects during the treatment. My anemia got worse and I needed a transfusion to get my hemoglobin and hematocrit back up. And I developed a cough that lasted for weeks. But overall it was pretty easy, looking back on it.

Now I feel great. All my blood cell counts have returned to normal, except that I have low numbers of lymphocytes, but that's the whole idea behind the treatment. My hemoglobin, platelets, neutrophils, and everything else is absolutely fine.

A few years back, I thought the future was not so bright. The treatment options were limited. But now it looks like there is really going to be a big change in the way that CLL is treated. In addition to obinutuzumab, several other drugs have been approved by the FDA as treatments for CLL in recent months. None of these are curative, but they all seem very effective and I think these new treatments are going to have a significant effect on the natural course of the disease.

I am a pharmacologist myself, so I understand the science behind these drugs, but I still find them amazing. I think that with all the improvements and breakthroughs that are happening in science today, we are really on the cusp of eliminating cancer as we now know it.

A couple of years ago, my daughter asked me if she could also develop the type of cancer I have now. And I said yes, I suppose it is possible, but don't be concerned, because it is my firm belief that by the time you get to be my age, virtually all cancers will be either preventable, curable, or treatable, similar to how we can treat high blood pressure now. I really think we can look forward to that for the next generation.

Breakthrough therapy designation

was awarded to 18 anticancer drugs as of July 31, 2014, and five drugs have received FDA approval after being designated breakthrough therapies.

The FDA recently approved a second therapeutic with breakthrough therapy designation for the treatment of CLL. Ibrutinib (Imbruvica) is a therapeutic that targets Bruton agammaglobulinemia tyrosine kinase (BTK), which is a protein that is one component of a signaling pathway that promotes the survival and expansion of CLL B cells. Ibrutinib was designated a breakthrough therapy for CLL in April 2013 and approved by the FDA for this use just 10 months later, after early stage clinical trials showed that the majority of patients with CLL responded to the therapeutic for an extended period (90).

Additional large-scale, randomized clinical trials are needed to confirm that the dramatic responses seen in patients with CLL who are being treated with ibrutinib translate into extended survival. These studies are underway. In fact, data from one of these trials showed that when compared with ofatumumab, ibrutinib significantly lengthened the time to disease progression and overall survival for patients with CLL (91).

After receiving breakthrough therapy designation for the treatment of MCL, a form of non-Hodgkin lymphoma, in February 2013, ibrutinib was approved by the FDA for this use just nine months later. Similar to CLL, MCL arises in B cells that are particularly dependent on the BTK signaling pathway for survival and expansion. Blocking BTK with ibrutinib effectively shrank tumors in the majority of patients with MCL (92). MCL patients have a particularly poor outlook, and it is hoped that longer follow-up of these patients will reveal that ibrutinib not only dramatically shrinks MCL tumors but also extends survival.

Ibrutinib is also being tested in clinical trials as a treatment for a number of other types of blood cancer originating in B cells that depend on BTK: diffuse large B-cell lymphoma, follicular lymphoma, multiple myeloma, and Waldenström macroglobulinemia. In the case of Waldenström macroglobulinemia, ibrutinib has been designated a breakthrough therapy by the FDA because it has shown tremendous benefit to patients with this rare disease, such as **Shelley Lehrman** (see p. 58). Determining if treatments for a certain cancer might benefit patients with other types of cancer improves patient care and increases the return on prior investments in cancer research.

Idelalisib (Zydelig) is another molecularly targeted therapeutic that had breakthrough therapy designation for the treatment of CLL and some forms of non-Hodgkin lymphoma. Idelalisib targets phosphatidylinositol 3-kinase (PI3K) delta, a component of a second signaling pathway that promotes survival and expansion of the B cells affected in these diseases. Early clinical trial results were extremely promising (93, 94), and in July 2014, the FDA approved idelalisib for the treatment of CLL and two forms of non-Hodgkin lymphoma: follicular B-cell non-Hodgkin lymphoma and small lymphocytic lymphoma.

Two Approaches to Address Treatment Resistance

Despite the major advances we have made in treating cancer, some cells in a tumor are not completely eliminated by the therapies we currently use, and over time, a disease may continue to progress. This is referred to as treatment resistance.

Resistance to treatment occurs in two ways: acquired resistance, which develops during the course of a given treatment, and innate resistance, which is present even before a certain treatment begins. There are many molecular reasons for treatment resistance, making it one of the greatest challenges that we face today when caring for patients with cancer (see sidebar on **The Challenge of Treatment Resistance**, p. 57).

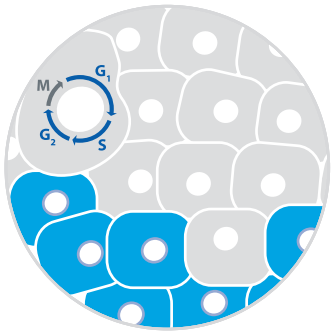
Two FDA decisions in the first four months of 2014 have helped address the problem of treatment resistance for a group of patients with lung cancer and for some patients with melanoma.

In April 2014, the FDA approved a molecularly targeted therapeutic called ceritinib (Zykadia) for patients with NSCLC that has become resistant to another molecularly targeted therapy, crizotinib.

Both crizotinib and ceritinib block the function of a signaling protein called ALK, which drives about 5 percent of cases of NSCLC. Although crizotinib benefits many patients with NSCLC driven by ALK, not all patients respond (95). Moreover, the majority of patients who

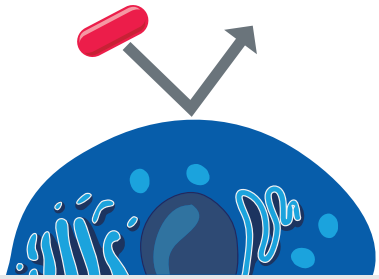
THE CHALLENGE OF TREATMENT RESISTANCE

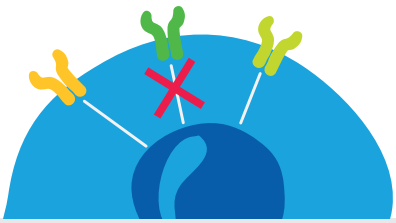
Diversity, or heterogeneity, among cancer cells within and between tumors, is ultimately what drives insensitivity to treatment, which in turn leads to treatment resistance. Some examples of heterogeneity are as follows:



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.

initially respond eventually relapse because their cancer has become resistant to crizotinib (95).

NSCLC resistance to crizotinib occurs through a variety of molecular mechanisms, including the emergence of new mutations in ALK (96) (see sidebar on **The Challenge of Treatment Resistance**). Recent research has shown that ceritinib is able to block many of the unique forms of ALK that result from these new mutations (97). In this way, ceritinib benefits many patients, like **James (Rocky) Lagno** (see p. 62), with crizotinib-resistant NSCLC driven by ALK (98).

SHELLEY LEHRMAN
AGE 50
SOLON, OHIO

"I have been taking it [ibrutinib (Imbruvica)]... and I feel great, my life is as busy and full as it was before my diagnosis."

About 1500 people are diagnosed each year in the United States with **Waldenström macroglobulinemia.**

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BEATING WALDENSTRÖM MACROGLOBULINEMIA THANKS TO IBRUTINIB

When I was diagnosed with Waldenström macroglobulinemia in 2011, I was shocked. I was just 47, with three kids, a great husband, a crazy dog, and a busy life. After my disease failed to respond to the first treatment assigned to me through a clinical trial, I immediately enrolled in a second clinical trial. I was assigned ibrutinib (Imbruvica) as part of this trial and have been taking it ever since, and I feel great. My life is as busy and full as it was before my diagnosis.

My journey with cancer began in February 2011. While showering, I noticed a few lumps in my neck that hadn't been there before. I wasn't really worried, thinking they were pimples or something else that would soon go away. But they didn't go away. So, when I saw my primary care physician for my annual physical the following month, I asked her to check them. She didn't think they were anything to worry about either, but I knew something wasn't right and asked her to order some follow-up tests.

A CT (computerized tomography) scan of my neck and chest revealed that I had enlarged lymph nodes. However, after follow-up blood tests, the conclusion of a staff review of all the information was that we should hold off on any treatments because a virus may have caused the enlarged lymph nodes. It was hoped that my symptoms would disappear, but they didn't. As a result, in June 2011, I had a biopsy of the lymph nodes and bone marrow. The biopsy results showed that I had Waldenström macroglobulinemia.

I had no idea what Waldenström was. My local oncologist told my husband and me more about the disease and recommended that I immediately start treatment with bortezomib (Velcade). We listened, and went home and researched the treatment. We learned that bortezomib had a lot of side effects, so we did more research. This led us to Dr. Treon at the Dana-Farber Cancer Institute in Boston.

At our first visit to Dana-Farber in September 2011, we were told that the best approach would be to watch my symptoms and wait. However, by our second visit, in January 2012, I was feeling tired all the time and the markers of disease in my blood showed that my condition had deteriorated. Dr. Treon told us it was time to do something and suggested I enroll in a clinical trial testing carfilzomib (Kyprolis) together with rituximab (Rituxan).

After a number of rounds of carfilzomib and rituximab, the side effects I was experiencing started mounting and my disease wasn't responding. So, in June 2012, I discontinued the trial.

At Dr. Treon's recommendation, I immediately enrolled in a clinical trial testing ibrutinib. I went home with a month's supply of pills and the next morning started taking them. Within days, my energy had increased, and at my one-month checkup, all the markers of disease in my blood showed improvement and I hadn't felt so good in a long time.

I am still taking ibrutinib and have follow-up visits every three months. I feel apprehensive at each of these visits, but so far, so good. I continue to do well. I have my down days, but after hugging my kids and husband a little bit tighter, I keep going.

Participating in clinical trials was an easy decision for me. I feared my loved ones could be stricken with the same disease in the future, and I knew that by taking part I was doing something that could potentially benefit them. I also felt that I had more control over my health care because the clinical trials gave me choices fueled by the most recent research.

I am so thankful for the opportunity to take part in clinical trials. At my first checkup after being assigned ibrutinib, Dr. Treon thanked me for taking part in the trial, and it was then I realized that researchers need participants as much as participants need researchers, and that this is the way cancer will be cured.

In January 2014, the FDA approved the combination of trametinib (Mekinist) and dabrafenib (Tafinlar) for the treatment of certain forms of melanoma, the most aggressive form of skin cancer. This is the first time that two molecularly targeted therapeutics have been approved by the FDA as a combination treatment for the same disease. It is expected that combinations of molecularly targeted therapeutics will become an integral part of treatment in the near future as our understanding of cancer biology increases (see **What Progress Does the Future Hold?**, p. 80).

About 50 percent of melanomas are driven by an abnormal protein called BRAF V600E (99). This knowledge led to the development and subsequent FDA approval of two BRAF V600E–targeted drugs, vemurafenib (Zelboraf) and dabrafenib (Tafinlar). Because of their specificity, these drugs are FDA approved only for the treatment of patients with metastatic melanoma who have the BRAF V600E protein, as determined by specific tests or companion diagnostics (see sidebar on **Companion Diagnostics**). However, recent results from a large clinical trial indicate that vemurafenib may also benefit patients with metastatic melanoma driven by a second abnormal BRAF protein, BRAF V600K (100).

Trametinib blocks the activity of two proteins, MEK1 and MEK2, that function in the same signaling network as abnormal BRAF proteins. Trametinib is FDA approved for the treatment of metastatic melanoma driven by either BRAF V600E or BRAF V600K. As with vemurafenib and dabrafenib, patients must test positive for one of these mutations before beginning treatment with trametinib.

Although vemurafenib, dabrafenib, and trametinib benefit many patients with melanoma driven by abnormal BRAF proteins, some patients never respond to these therapeutics, whereas the majority of those who initially respond relapse within approximately one year of starting treatment owing to treatment resistance (99, 101, 102). Because dabrafenib and trametinib block different components of the same signaling network, it was thought that together they might eliminate the emergence of resistance (103). In fact, clinical trial results show that the combination almost doubles the length of time before metastatic melanoma becomes resistant to treatment and progresses (103).

COMPANION DIAGNOSTICS

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

- are stringently tested for their safety, 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 be spared any adverse side effects of the therapy.

Above and Beyond for Patients With Peripheral T-cell Lymphoma

The drugs crizotinib, ceritinib, dabrafenib, and trametinib, discussed above, target the aberrant proteins driving some forms of lung cancer and melanoma that result from specific genetic mutations. However, research has shown that changes in the chemical tags on the DNA itself, or on the proteins around which the DNA is wrapped, as well as mutations within the proteins that read, write, and/or erase these tags, can also lead to cancer. Collectively, these tags are referred to as the epigenome, and it functions to control how the various genes are read (see sidebar on **Genetic and Epigenetic Control of Cell Function,** p. 10). Importantly, the epigenome is dynamic and can be changed by cells as needed. It can also be altered by drugs that target its readers, writers, and erasers. In fact, the FDA has already approved four drugs that target two such types of epigenome-modifying proteins. This expanding class of drugs is emerging as an exciting new avenue of attack on cancer, particularly because early indications are that some of the cancer-induced changes to the epigenome may be reversible.

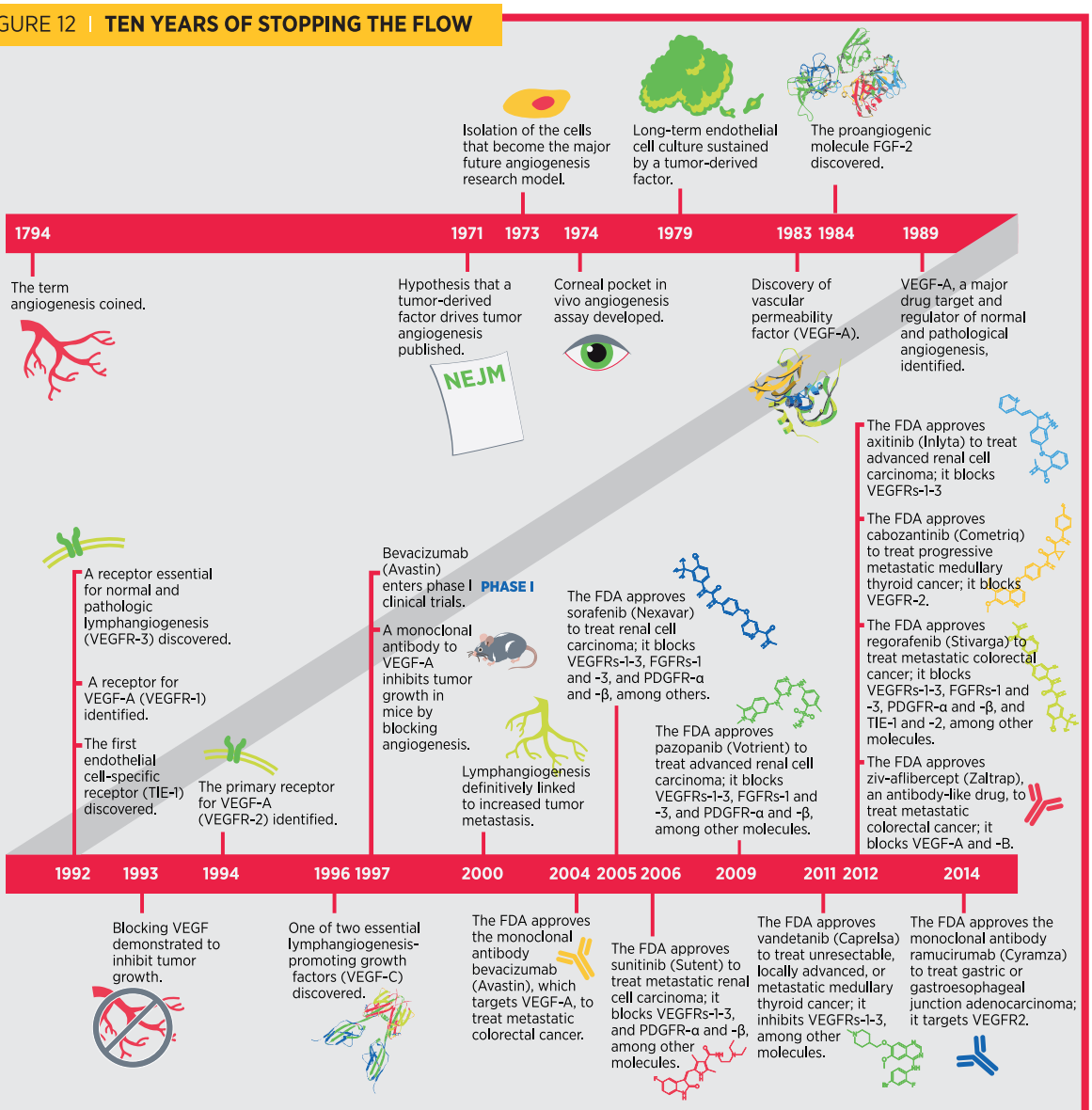
Among the many chemical tags included in the epigenome is a class of tag called acetyl groups. These tags can be added or removed from the histones around which the DNA is wrapped by proteins called histone acetylases or deacetylases, respectively. In July 2014, the FDA approved belinostat (Beleodaq), which targets multiple types of histone deacetylases, for the treatment of patients with

peripheral T-cell lymphoma who had become resistant to or had relapsed on prior therapies. This decision was based on clinical trial results showing that belinostat was effective in more than 25 percent of patients, many of whom had received numerous prior therapies. It therefore offers a new treatment option for the 7,000 to 10,000 individuals anticipated to be diagnosed with peripheral T-cell lymphoma in 2014, most of whom will become resistant to their initial therapy.

New Option for Blocking Blood Supply to Tumors

Research has shown that many solid tumors are dependent on the growth of new blood and lymphatic vessels to grow and survive. It has also led to the identification of many molecules that control these processes, as well as the development of anticancer therapies that specifically block these molecules. In fact, in the past 10 years, the FDA has approved 10 such therapeutics, which are called antiangiogenic agents (see **Figure 12**).

FIGURE 12 | **TEN YEARS OF STOPPING THE FLOW**



In the past 10 years, the U.S. Food and Drug Administration (FDA) has approved 10 anticancer therapeutics that work by blocking the development of new blood vessels (angiogenesis). Bevacizumab (Avastin) was the first of these drugs, known as antiangiogenic agents, to be approved, in 2004, and ramucirumab (Cyramza) is the most recent, in 2014. Research into the processes of angiogenesis and lymphangiogenesis, in both normal and pathological conditions including cancer, helped identify many of the molecular regulators of these processes, and these regulators are the specific targets of the 10 antiangiogenic agents. The first date of approval for each of these therapeutics is indicated on the timeline; however, most of these agents received approval from the FDA for the treatment of additional cancers in subsequent years. Pathological angiogenesis also underlies neurovascular age-related macular degeneration, a major cause of blindness. Two antiangiogenic agents—ranibizumab (Lucentis), a derivative of bevacizumab (Avastin), and aflibercept (Eylea)—are FDA approved for the treatment of this form of eye disease and may be approved for other forms in the near future. Thus, cancer research can benefit patients with diseases other than cancer.

SURVIVING LUNG CANCER THANKS TO MODERN MEDICINE

I have lung cancer caused by a rare genetic mutation. I was so sick the doctors warned me I probably had only about a year to live. But I received a drug that targets my specific mutation, and now I am pretty much back to normal. For me, it's like a miracle.

My experience with cancer started around Thanksgiving 2010, with a dry, persistent cough that wouldn't go away. I saw several specialists, but no one mentioned cancer. I am not a smoker; I've never smoked. So I guess that's why the doctors didn't think of it.

Finally, it got to the point that I had no energy and couldn't catch my breath. I went to an urgent care facility, and the staff there thought it was pneumonia. Then I started coughing up a little blood. I went back to the urgent care facility, and a doctor there suggested it could be lung cancer. I got the diagnosis in July 2011.

That was a shock. It was very upsetting to my wife and me. We'd been married less than two years, and this was obviously going to have a big impact on our life together.

After I had my first appointment with an oncologist, it turned out that not only did I have primary lung cancer, but I also had primary cancer of my thyroid (which was later removed). The oncologist told me I should probably think about a bucket list but also suggested I should get a second opinion. So I went to a hospital in Boston, where they started me on intravenous chemotherapy and an aggressive course of radiation. I had daily radiation for more than 30 treatments in my chest area, so much radiation that I had burns on my back.

My wife, Geralynn, had done a lot of research and had learned about a clinical trial for patients with the ALK mutation and lung cancer. We wanted to know if I could get into it. The doctors, however, thought the standard-of-care treatment was the way to go. So we stuck with that. But then the scans showed that the tumors were actually getting bigger. I was told I should get my affairs in order because a patient in such a situation has, on average, about 13 months to live.

Geralynn insisted that I have another biopsy and genetic testing to see if I had the ALK mutation and—lo and behold—I did. So I started taking the drug crizotinib, which had recently been approved as a treatment for ALK-positive lung cancer. It worked well for several months in controlling the tumors, but then it was no longer effective. By that point I was so tired I couldn't walk the dogs. My oncologist suggested I contact Dr. Alice Shaw at Massachusetts General Hospital, who was conducting a clinical trial of another drug targeting ALK, ceritinib.

As part of the protocol, I had an MRI, which showed lesions in my brain. That and the history of thyroid cancer kept me out of the regular clinical trial, but Dr. Shaw obtained ceritinib for me on a compassionate use basis.

The first few weeks were rough because we had to get the dose right and there were some side effects, like nausea and other gastrointestinal issues. But then we got it straightened out, and since the middle of 2013, my condition has been stable. It's not a complete recovery and I don't have any expectation of going into remission or becoming cancer-free, but my quality of life is practically back to what I had before the diagnosis. I'm doing great.

It's a personal choice whether to enter a clinical trial. But let's face it, chemotherapy and radiation have been around for 40 years. You ought to see the new things that modern medicine can do.

JAMES (ROCKY) LAGNO
AGE 53
EPPING, NEW HAMPSHIRE

"I was so sick the doctors warned me I probably had only about a year to live... And now I am pretty much back to normal."

Over 159,000 individuals are expected to die from **lung cancer** in the United Sates in 2014

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The newest member of this growing class of therapeutics is ramucirumab (Cyramza). It was approved by the FDA for the treatment of metastatic gastric (stomach) cancer and cancer of the part of the esophagus that connects to the stomach (gastroesophageal junction adenocarcinoma) in April 2014. Patients with metastatic gastric cancer have a very poor outlook; just 4 percent survive five years (7). With such a clear need for new treatment options, the fact that ramucirumab extended overall survival for patients with metastatic gastric cancer in phase III clinical trials (104, 105) provides patients with new hope.

Ramucirumab is also being tested in numerous clinical trials as a potential treatment for other types of cancer. Recent results from one of these trials showed that ramucirumab significantly prolonged survival for some patients with the most deadly form of lung cancer, NSCLC (106). If these data result in an FDA approval, this will provide more patients with new treatment options and increase the return on prior investments in cancer research.

New Path to Approving Breast Cancer Therapeutics

Breast cancer is the second leading cause of cancer-related death for women in the United States (1). Studies have shown that intervening early and aggressively can improve survival for breast cancer patients who have a high risk of recurrence. Therefore, the FDA outlined a new path for regulatory approval of breast cancer therapeutics in May 2012 (107) (see sidebar on **New FDA Approach to Breast Cancer Therapeutics**).

In September 2013, pertuzumab (Perjeta) became the first therapeutic approved under this new regulatory path.

Pertuzumab is a therapeutic antibody that targets the HER2 protein. About one in every five of the 235,030 cases of breast cancer anticipated to be diagnosed in the United States in 2014 will overexpress HER2 (1, 109).

The FDA decision allows pertuzumab to be used as part of a presurgery course of treatment for certain patients with HER2-positive, early stage breast cancer. The decision was based on clinical trial results showing that women who received pertuzumab in addition to trastuzumab and the traditional chemotherapy docetaxel before breast cancer surgery were significantly more likely to have no residual invasive cancer detected in breast tissue and lymph nodes removed during surgery compared with women who received only trastuzumab and docetaxel (110).

It is important to note that these data are preliminary and that we do not know for certain whether the pertuzumab-containing presurgery treatment will improve patients' long-term outcomes, including survival. To determine this, a large-scale clinical trial is ongoing and the results are expected in 2016.

Treatment With Immunotherapeutics

A new approach to cancer treatment that has begun to transform the lives of patients is immunotherapy.

Cancer immunotherapy refers to treatments that can unleash the power of a patient's immune system to fight cancer the way it fights pathogens. Not all cancer immunotherapies work in the same way (see sidebar on **How Immunotherapeutics Work**, p. 65). As our scientific understanding of the immune system and how it interacts with cancer cells increases, we can expect to see novel immunotherapies and new ways to use those that we already have.

Given that some patients have remarkable and durable responses following immunotherapy, this form of cancer treatment holds incredible promise for the future, potentially even cures for some patients. The progress is very recent, and most experimental cancer immunotherapies, which are the focus of the following discussion, are still in clinical development and have, therefore, not yet been approved by the FDA.

NEW FDA APPROACH TO BREAST CANCER THERAPEUTICS

Many patients with breast cancer are treated with a traditional chemotherapy and/or molecularly targeted therapy before surgery, an approach called neoadjuvant therapy. The goal of neoadjuvant therapy for breast cancer is to shrink a patient's breast tumor, rendering inoperable tumors operable and thus allowing breast conservation. If, after completing neoadjuvant therapy, no residual invasive cancer is detected in breast tissue and lymph nodes removed during surgery, a patient is said to have a pathologic complete response.

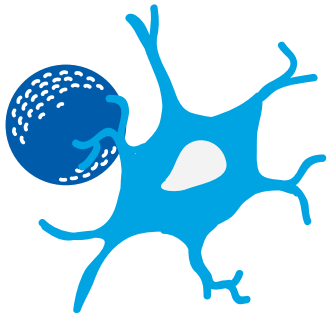
Research has shown that pathologic complete response correlates with long-term survival (108). As a result, the U.S. Food and Drug Administration (FDA) decided to use pathologic complete response as a reasonable endpoint to assess the likelihood that a neoadjuvant therapy will improve disease-free or overall survival for patients with breast cancer (107).

HOW IMMUNOTHERAPEUTICS WORK

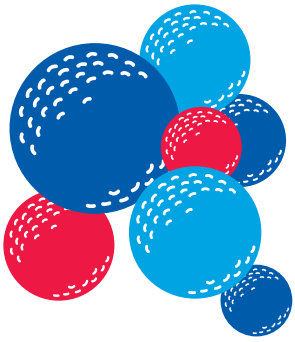
The way in which different immunotherapeutics work to benefit patients varies:

some release the brakes on the natural cancer-fighting power of the immune system, for example, **ipilimumab (Yervoy) and pembrolizumab.**

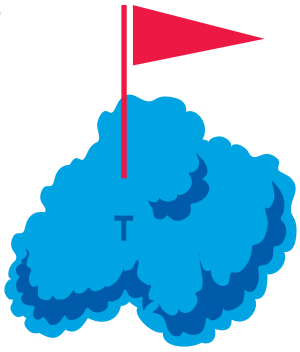
some enhance the cancer-killing power of the immune system by triggering the cancer-fighting T cells, for example, **DCVax-L.**



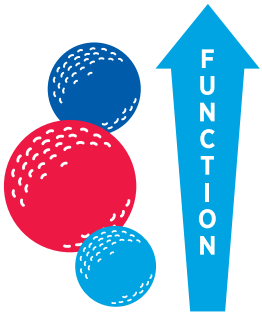
some boost the killing power of the immune system by providing more cancer-targeted immune cells called T cells; these are called **adoptive T-cell therapies.**



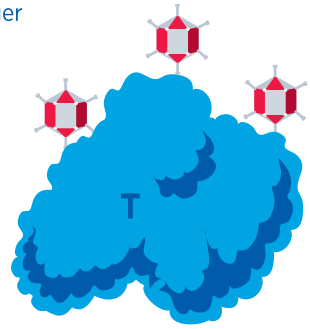
some flag cancer cells for destruction by the immune system, for example, **obinutuzumab.**



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



some comprise a virus that preferentially infects and kills cancer cells, releasing molecules that trigger cancer-fighting T cells; these are called **oncolytic virotherapeutics.**



Releasing the Brakes on the Immune System

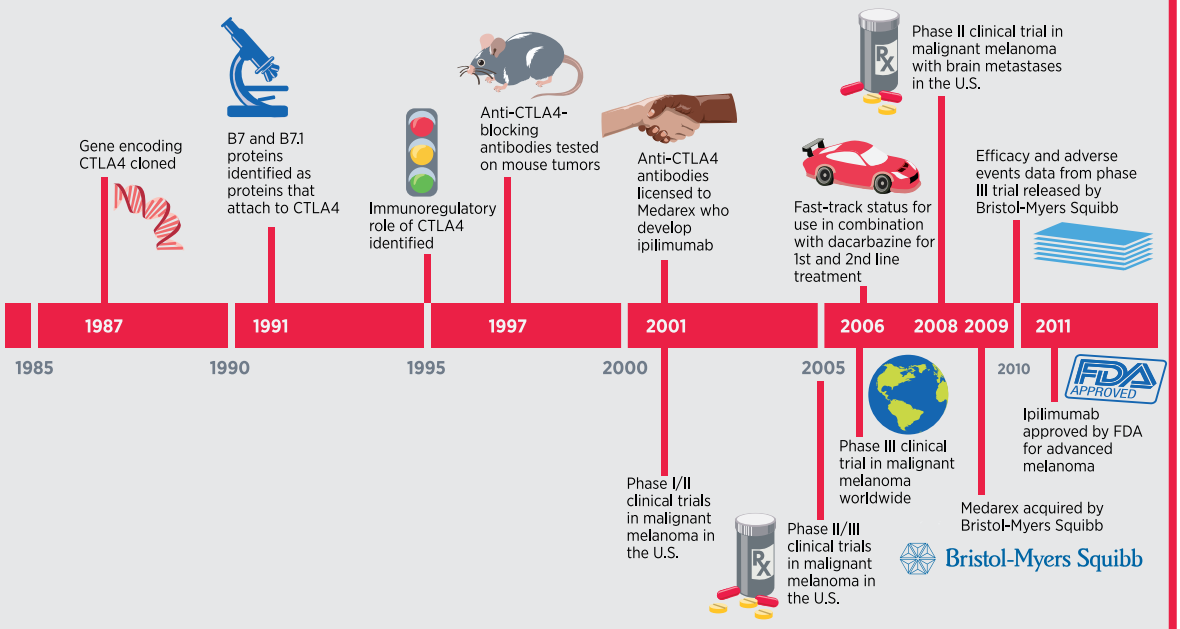
Cells called T cells are key players in the immune system that can naturally destroy cancer cells. However, tumors can prevent T cells from carrying out this function. For example, some tumors have high levels of proteins that can put the brakes on T cells, stopping them from attacking the cancer cells. The finding that these tumor proteins trigger T cells' brakes by attaching to complementary proteins, called immune checkpoint proteins, on the surface of T cells, led researchers to look for ways to disrupt these interactions.

Ipilimumab (Yervoy) is the only checkpoint inhibitor currently approved by the FDA; it targets the checkpoint protein CTLA4 and was approved for the treatment of metastatic melanoma in March 2011. This FDA approval, which followed almost 25 years of basic, translational, and clinical research (see **Figure 13**), has transformed the lives of many patients with metastatic melanoma, including Andrew Messinger (who was featured in the *AACR Cancer Progress Report 2013* (5)).

In some patients with metastatic melanoma, ipilimumab has yielded dramatic and durable responses (111). These spectacular responses paved the way for clinical trials, many of which are still ongoing, testing whether ipilimumab might also be effective against other forms of cancer. They also motivated researchers to rapidly develop therapeutics that target a second checkpoint protein, called PD-1, as well as therapeutics that target the protein on tumor cells that attaches to PD-1, PD-L1.

As a result of promising early results in a small clinical trial (112), the FDA granted one therapeutic antibody that targets PD-1, pembrolizumab (previously called both MK-3475 and lambrolizumab), breakthrough therapy designation for the treatment of metastatic melanoma. More recent data extend the initial results, with the majority of patients, like **Richard Murphy** (see p. 68), still gaining benefit from pembrolizumab more than one year after starting treatment (113). Large-scale clinical trials are currently ongoing to confirm these results.

FIGURE 13 | **STOPS ALONG THE WAY TO DEVELOPING THE FIRST CHECKPOINT BLOCKING AGENT**



Ipilimumab (Yervoy) is an immunotherapeutic that works by counteracting a brake on cancer-fighting immune cells called CTLA4. It is currently the only drug of its kind to be approved by the U.S. Food and Drug Administration (FDA). Almost 25 years of basic and clinical research underpinned the development of ipilimumab. The story began in 1987, when researchers discovered a gene they called CTLA4. It then took nearly eight years before the function of CTLA4 was uncovered, and another 16 years before this knowledge was translated into ipilimumab. Several other drugs in development target another immune-cell brake called PD1, and others target the tumor protein that steps on this brake, PD-L1. Adapted from (5).

Beyond melanoma, pembrolizumab is also being tested in clinical trials as a potential treatment for more than 30 other types of cancer. Results are not yet available for the majority of these. However, early results show that the immunotherapeutic benefits some patients with NSCLC and, potentially, some with head and neck cancer (114, 115), although these results are preliminary.

A second therapeutic antibody targeting PD-1, nivolumab, is also being tested in clinical trials as a potential treatment for numerous cancer types. Recent preliminary results show that nivolumab benefits some patients with advanced melanoma; it has been reported that more than 40 percent of patients are still gaining benefit from this therapeutic more than three years after starting treatment (116). Early results indicate that it may also benefit patients with NSCLC (117, 118), Hodgkin lymphoma, and renal cell carcinoma (119), which is the most common form of kidney cancer.

Recent promising early results from a small clinical trial showed that a therapeutic that targets PD-L1, MPDL3280A, could benefit patients with bladder cancer (120). As a result, the FDA granted MPDL3280A breakthrough designation for the treatment of bladder cancer.

No treatment advances

for bladder cancer have been made in nearly 30 years despite it being the ninth most common cancer worldwide.

Unfortunately, not all patients have dramatic responses following treatment with ipilimumab or a PD1-targeted therapeutic. To help increase the number of patients who may benefit from these therapeutics, researchers are assessing combinations of immunotherapeutics that target different checkpoint proteins and combinations of immunotherapeutics that work in different ways, as well as combining immunotherapeutics with other types of anticancer treatments, including molecularly targeted therapeutics.

To this end, recent remarkable results showed that 75 percent of patients with metastatic melanoma treated with a combination of ipilimumab and nivolumab were still benefiting two years after the start of treatment (121). In a second small clinical trial, early results showed that a combination of ipilimumab and an oncolytic virotherapeutic called talimogene laherparepvec benefited more patients with metastatic melanoma than either immunotherapeutic alone (122).

Enhancing the Killing Power of the Immune System

Another approach to cancer immunotherapy is to boost the ability of T cells to eliminate cancer cells. To return to the analogy of the car, this approach is like stepping on the accelerator, and it can be achieved in a number of ways, including the administration of adoptive T-cell therapy, a soluble molecule called a cytokine that can enhance T cell function, or a therapeutic cancer vaccine.

Adoptive T-cell therapies are complex medical procedures built upon our accumulating knowledge of the biology of cancer and the biology of the immune system. In these procedures, T cells are harvested from a patient, expanded in number and/or genetically modified in the laboratory, and then returned to the patient, where they attack and potentially eliminate the cancer cells. No FDA-approved adoptive T-cell therapies are yet available. Several approaches, however, are currently being tested for a number of types of cancer, one of which, called CTL019, recently received breakthrough therapy designation from the FDA for the treatment of ALL (see sidebar on **Types of Adoptive T-Cell Therapies**).

TYPES OF ADOPTIVE T-CELL THERAPIES

There are two main types of adoptive T-cell therapy.

Chimeric antigen receptor (CAR) T-cell therapy. T cells are harvested from blood or bone marrow and genetically modified before being expanded in number. This modification targets the T cells specifically to the patient's cancer and triggers them to attack when they get there.

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

BEATING STAGE IV MUCOSAL MELANOMA THANKS TO IMMUNOTHERAPY

When I was diagnosed with metastatic melanoma, there were very few treatments to choose from, and after standard treatment failed to control my disease, I took part in two clinical trials. I wasn't able to finish either trial, but the medication I received through the second one, an anti–PD-1 immunotherapy, worked anyway and my tumors are gone. I've been stable for two years. The experimental immunotherapies changed my life and allowed me to look further down the road. After I was diagnosed, I just hoped I'd see my youngest daughter go to kindergarten. Now maybe I can see her get married.

It began in 2008, when my nasal passages were blocked. The ENT [ear, nose, and throat] doctor looked and said, "You've got a golf ball up there." He did a biopsy and called a week later with a diagnosis of mucosal melanoma.

I'd never heard of it, but I soon learned that it's very rare, accounting for only about 1 percent of melanoma cases. Unfortunately, the prognosis is usually not good. The treatment was to remove the tumor and then treat the area with radiation, five days a week for 10 weeks.

A year later, a tumor showed up in my lung, and the doctors removed it. I remember sitting with my wife, saying, "All right, this is not that bad—I can manage it if every couple of years I have to go under the knife." Unfortunately, the situation did not stay that way. The cancer spread to my spine and midsection, and scans showed that I had cancer in 15–20 sites.

My oncologist did everything he could, but finally he said, "There is no more conventional medicine that can help you. We should consider clinical trials." For me, it was an easy choice because there wasn't anything else to do.

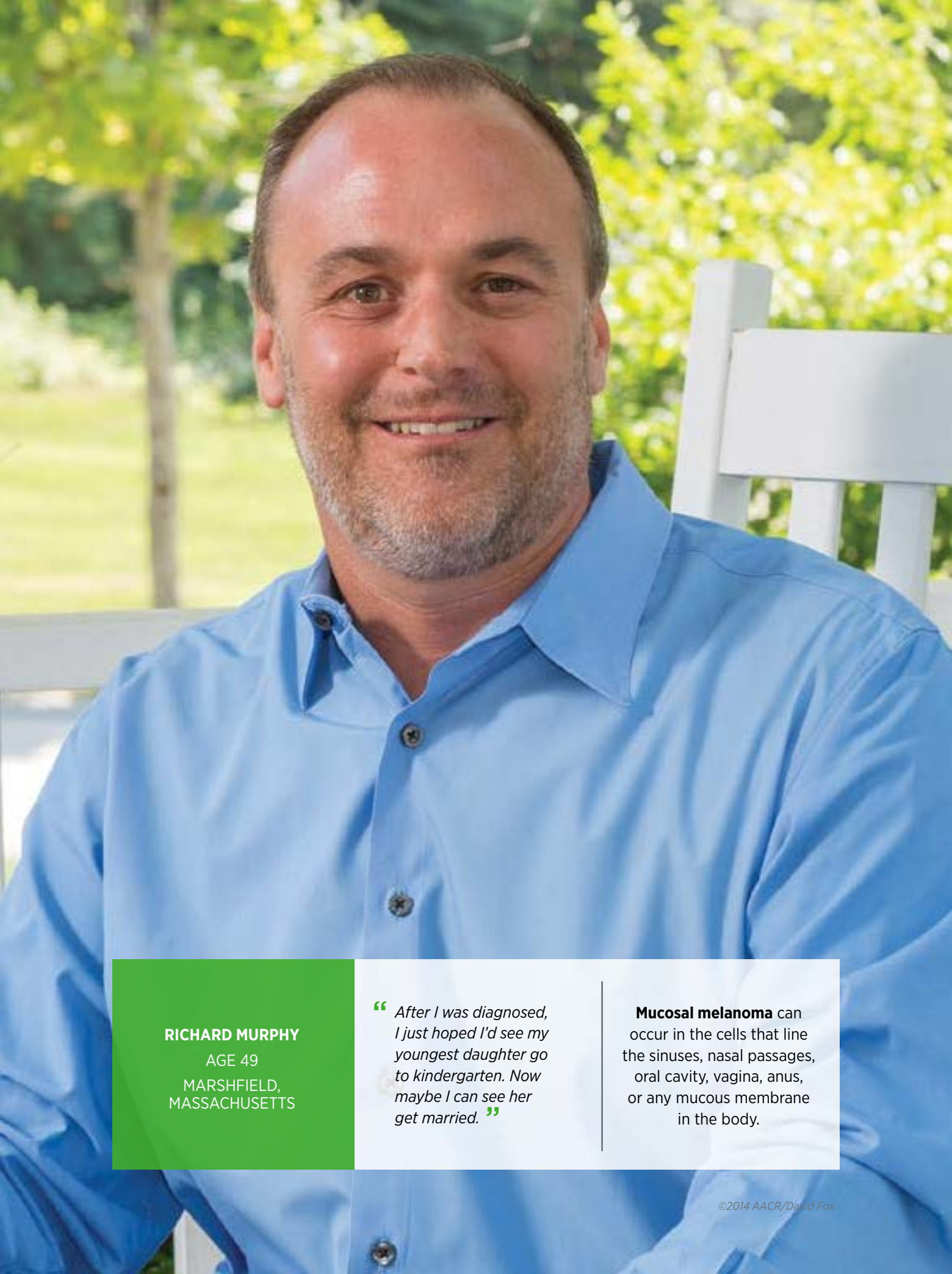
In February 2011, I started in a trial for ipilimumab, which allows the T cells in your body to attack your cancer. After several infusions of the drug, scans showed that my tumors had shrunk by 20 percent. That was the first good news we'd had since 2008. During my time in the trial, the FDA [U.S. Food and Drug Administration] approved the drug and it was marketed as Yervoy, so my last couple of doses were not through the trial. Ipilimumab worked well for a while, but then the tumors grew again and the doctors took me off the drug ahead of schedule.

My doctor told me that new drugs called anti–PD-1 immunotherapies were coming out. PD stands for "programmed death," which isn't a great name, but the drugs that target it basically restore the natural ability of the immune system to go after cancer cells.

I was turned down for one trial but was accepted into another sponsored by Merck, with an anti–PD-1 drug then called MK-3475. I started on March 1, 2012. It was an all-day infusion every three weeks. But after only five infusions, the doctors thought I was going into renal failure. So they put me in the hospital for three days and took me off the drug. That was a tough time.

The doctors then did an ultrasound of my kidneys. My doctor called me to say they couldn't figure out what was going on with my kidneys, but the ultrasound showed some of the tumors, and they were all shrinking. A few weeks later, I had a full set of scans, and the tumors had shrunk by 50 percent. A few months after that, all they could see was shadowing, which means that something was there once but it really isn't there anymore. It has stayed that way, nothing there, after only five infusions. It's amazing.

The reality is that without cancer research, I wouldn't be here. I want to help the next person and keep the cause going, so I give speeches to support more funding for research. My wife and I also participate in triathlons to raise money for research: I swim for money. Our team, Tri-ing for a Cure, has raised over $100,000.



RICHARD MURPHY
AGE 49
MARSHFIELD, MASSACHUSETTS

"After I was diagnosed, I just hoped I'd see my youngest daughter go to kindergarten. Now maybe I can see her get married."

Mucosal melanoma can occur in the cells that line the sinuses, nasal passages, oral cavity, vagina, anus, or any mucous membrane in the body.

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CAR T-cell therapy has been particularly successful for adults with CLL and for adults and children with ALL (123-125). In fact, a recent study indicates that 86 percent of pediatric patients with ALL experienced complete remissions, and one patient remains in remission 20 months after initiating treatment (126). Although this therapy is promising, some children eventually relapse.

Researchers are currently working to develop CAR T cells that will target other types of cancer, including acute myeloid leukemia, multiple myeloma, and some solid tumors, but the research is in the very early stages (127, 128). As research continues to increase our understanding of why CAR T-cell therapy does not work for all patients, new and more effective CAR T-cell therapies are likely to emerge in the future (128).

Tumor-infiltrating lymphocyte therapy (TIL therapy) is an experimental approach primarily used to treat patients with metastatic melanoma. Since its development 12 years ago (129), it is estimated that durable responses occur in about one in every five patients with metastatic melanoma and that many of these individuals, like Roslyn Meyer (who was featured in the *AACR Cancer Progress Report 2011*), have ongoing responses (130).

Until recently, TIL therapy has largely been limited to the treatment of melanoma. However, new reports indicate that it may be causing tumor regression for one patient with bile duct cancer and complete, ongoing responses for two patients with cervical cancer (131, 132). Thus, TIL therapy may one day benefit patients with a wide range of cancer types.

The majority of patients treated with TIL therapy also receive high doses of the cytokine IL-2 to give the transferred T cells a boost, and it is the IL-2 that causes the most severe adverse effects of the treatment. Researchers are investigating a number of ways to overcome this problem, including engineering less toxic forms of IL-2 (133). This is important because even though IL-2 was approved by the FDA to treat metastatic melanoma and renal cell carcinoma in 1998, it is not used very often because of its toxic, even lethal, side effects. When it is used, however, recent results show that high-dose IL-2 can lead to durable responses (134, 135).

Therapeutic cancer vaccines enhance the killing power of the immune system by training the patient's T cells, while they are inside the patient's body, to recognize and destroy the patient's cancer cells. The development of these immunotherapeutics is an intensively studied area of cancer research. In fact, in the United States alone, several hundred ongoing clinical trials are testing therapeutic cancer vaccines.

One therapeutic cancer vaccine being tested as a treatment for the most aggressive form of brain cancer, glioblastoma multiforme (GBM), in a large-scale clinical trial, after showing promise in early stage clinical trials, is DCVax-L (136). DCVax-L is a cell-based vaccine whereby each patient receives a customized treatment that uses dendritic cells from his or her own body to boost cancer-fighting T cells. As a result of the immense potential of this immunotherapeutic, in March 2014, the Paul Ehrlich Institute—the German equivalent of the FDA—approved the use of DCVax-L for the treatment of patients with GBM and less aggressive forms of the disease through an early access program.

Cytokines

are molecules naturally released by immune cells that alter the function of other immune cells. Cytokines such as interleukin 2 (IL-2) boost T-cell function, including the ability to eliminate cancer cells.

Living With or Beyond Cancer

As a result of advances in cancer research, more people are surviving longer and leading fuller lives after a cancer diagnosis than ever before. In fact, the number of U.S. residents living with, through, or beyond cancer is estimated to have risen to almost 14.5 million, compared with just 3 million in 1971 (2, 3). This 14.5 million includes an estimated 379,112 individuals who, like **Jameisha (Meisha) Brown** (see p. 72), received their cancer diagnoses as children or adolescents (ages 0–19) (1). These individuals are considered cancer survivors, although it is important to note that not all people who have received a cancer diagnosis identify with this term.

Glioblastoma Multiforme (GBM)

patients have a poor prognosis and usually survive about 15 months following diagnosis (137).

Three distinct phases are associated with cancer survivorship: the time from diagnosis to the end of initial treatment, the transition from treatment to extended survival, and long-term survival. Recent and promising progress realized for individuals in the first group was discussed in the previous two sections of the report (see **Treatment With Molecularly Targeted Therapeutics**, p. 52, and **Treatment With Immunotherapeutics**, p. 64). Here, the discussion focuses on advances made for those in the latter two groups, as well as the numerous challenges they face.

Each distinct phase of cancer survivorship is accompanied by a unique set of challenges (see sidebar on **Life After Initial Cancer Treatment Ends**). 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. 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.

LIFE AFTER INITIAL CANCER TREATMENT ENDS

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 their cancer diagnosis and treatment. Some of these challenges may 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 (3).

bone density loss (osteoporosis);

cognitive impairment sometimes referred to 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 very severe and often not relieved by rest;

FEAR

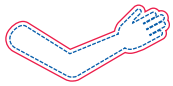
fear of cancer recurrence;

heart damage (cardiotoxicity);

INFERTILITY

infertility;

lung (pulmonary) damage;



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

pain;

premature aging;

recurrence of original cancer; and

SEXUAL DYSFUNCTION

sexual dysfunction.

While all cancer survivors potentially face critical health-related problems, pediatric cancer survivors (ages 0–14 at diagnosis) are particularly at risk because their bodies are still developing at the time of treatment. Adolescents (ages 15–19) and young adults (ages 20–39) also have to confront a distinctive set of concerns, including adapting to long-term cancer survivorship while beginning careers and thinking about starting families of their own.

SIXTEEN-YEAR CHILDHOOD CANCER SURVIVOR AND CANCER HEALTH DISPARITIES RESEARCHER

I was diagnosed with Burkitt lymphoma in June 1998. Cancer has caused me many difficult moments in life; there were even times when my doctors didn't know if I would make it. However, cancer brought out the best in me, and thanks to the team of doctors who help me manage the side effects of my treatments, I am studying for a master's degree in health studies and hope that one day I'll have a faculty position alongside the doctors who helped make my cancer history.

My journey with cancer started when I was just 8 years old, a few weeks into the summer after I finished second grade. I was experiencing abdominal pain and nausea, and I was really, really tired. My mom knew something wasn't right and took me to the pediatrician. During the exam, I noticed the pediatrician was paying a lot of attention to one particular area of my stomach, and then he started talking to my mom in hushed tones. He told her that he wanted me to have an emergency CT scan and have the results read that day.

We had the scan and then went back to the pediatrician. After he performed another physical exam he asked my mom to speak to him outside the room. I knew at that point that it must be bad. I overheard the doctor tell my mom she had to choose which hospital she wanted me to be treated at on the spot. She chose The University of Texas MD Anderson Cancer Center, and after going home to pick up some things, we went straight there.

After three days of tests, I had emergency surgery to remove some of the tumors around my small intestine, colon, ovaries, and appendix. I think it was after this first surgery that it really hit me: What was I going to face? What was the future ahead for me?

I was anxious to get answers to these questions and to try and understand what cancer and lymphoma meant, because these two words were used interchangeably. At first, it was hard for my child-like mind to understand cancer, but the doctors took the time to explain everything to me—they were very good. They used teddy bears, puppets, and dry-erase pictures to satisfy my curiosity and push for information. I learned a lot about the science of cancer at a very young age.

My initial treatment lasted just over eight months. I had multiple surgeries, including a small bowel resection and an appendectomy. I have a 10-inch incision in my abdomen that was opened twice to remove some tumors. I also had a number of chemotherapies; one regimen that was particularly hard was called R-CHOP [rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone]. All the kids in the hospital called doxorubicin "red devil" because of what it did to us. We all knew that if one of our friends had it on their pole it would be a while before we would be playing with them again.

Throughout my treatment I had a feeding tube because I couldn't tolerate any regular food by mouth except for yogurt and ice pops. I still have GI [gastrointestinal] problems as a result of my treatments, and I have scrupulous dietary restrictions because I can't digest foods.

During my treatment I was able to keep up with my schoolwork. There was a hospital school program at MD Anderson and a teacher from my school came to my house when I couldn't make it there. However, I remember a time when I couldn't get out of bed and one of my teachers persuaded me to come down to the classroom because she didn't want me to fall behind. It made me understand how important education is and that it gives people opportunities to do great things with their lives.

My doctors have been unable to find any evidence of cancer since February 1999, but I have had to learn to live with the side effects of the treatments I received. This has been a challenge, and there was a time when I missed three months of high school because of the pain. The side effects also affected my relationships in high school. The other children couldn't relate to the fact that I was taking more than 20 medications and still felt tired a lot of the time. I didn't let it keep me down, however, and cancer has actually given me more positives in life than negatives.

Now, I'm doing really well, I finished college and am pursuing a master's degree in health studies with a focus on cancer health disparities. I still see five specialty oncologists at MD Anderson every two months and a few doctors outside MD Anderson who help manage the long-term side effects of my cancer treatments, like my GI issues, neuropathy, and osteoarthritis, for which I wear a knee brace. This great interdisciplinary team of doctors has a patient-centered approach to care, and the fact that I feel they are listening to me has really improved the quality of my life.

Cancer definitely shaped my outlook on life, but it helps me to know that it could have been worse—I could have passed away like so many of my friends did. Instead, I was given another chance at life, and I hope that I can give back through my research to help make sure that equitable health care, prevention, and early detection programs are accessible to all.

JAMEISHA (MEISHA) BROWN
AGE 24
HOUSTON, TEXAS

"I was given another chance at life, and I hope that I can give back through my research to help make sure that equitable health care, prevention and early detection programs are accessible to all."

Approximately 19% of the 1,040 children and adolescents estimated to be diagnosed with **non-Hodgkin lymphoma** in 2014 will be diagnosed with **Burkitt lymphoma.**

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More than 108,000

cancer survivors ages 0–19 live in the United States (3).

19 Million

cancer survivors are projected to be living in the United States on Jan. 1, 2024 (3).

Among the 1.6 million U.S. residents projected to receive a cancer diagnosis in 2014 are approximately 16,000 children and adolescents (1). Fortunately, the overall five-year survival rates for children and adolescents diagnosed with cancer are currently 83 and 85 percent, respectively, and survivors of cancer diagnosed by the age of 19 account for almost 3 percent of the U.S. cancer survivor population (3). However, as discussed by **Congressman Michael McCaul** (see p. 76), these individuals face particularly demanding challenges. In fact, a recent study found that 98 percent of adult survivors of childhood cancer had one or more chronic health conditions, and 68 percent have severe/disabling or life-threatening conditions (138).

Given that cancer survivors who received their diagnoses as children or adolescents are at extremely high risk for long-term and late treatment-related side effects, the Children's Oncology Group, an NCI-supported clinical trials group that cares for more than 90 percent of these individuals, developed guidelines for their long-term care (see sidebar on **Guidelines for Long-term Follow-up of Survivors of Childhood, Adolescent, and Young Adult Cancers**).

GUIDELINES FOR LONG-TERM FOLLOW-UP OF SURVIVORS OF CHILDHOOD, ADOLESCENT, AND YOUNG ADULT CANCERS

The Children's Oncology Group "Long-Term Follow-Up Guidelines for Survivors of Childhood, Adolescent, and Young Adult Cancers" provide recommendations for screening and management of late effects that may arise as a result of treatments received by survivors who were diagnosed with cancer as a child, adolescent, or young adult. The guidelines were developed to help standardize and enhance the life-long follow-up care of these individuals.

Central to the guidelines is the idea that prevention and/or early identification of complications are vital if we are to decrease the long-term health risks associated with treatments for childhood, adolescent, and young adult cancers. As such, the guidelines indicate that the key services offered by a long-term follow-up program should include:

- **monitoring for and managing physical late effects;**
- **providing health education to survivors regarding their diagnoses, treatment exposures, and potential late effects;**
- **providing referrals to specialists and resources as indicated;**
- **encouraging wellness and health promotion activities;**
- **addressing psychosocial needs of survivors and affected family members;**
- **assessing and providing intervention for educational and/or vocational needs;**
- **assisting with financial and insurance issues;**
- **guiding transition from pediatric to adult-focused health care;**
- **empowering survivors to advocate for their own health care needs; and**
- **facilitating survivorship research.**

For more information on these guidelines, see http://survivorshipguidelines.org/

Individuals who receive a cancer diagnoses as children or adolescents, or young adult are not the only group extremely vulnerable to treatment-related health issues. The elderly are also particularly susceptible to the toxic effects of many treatments for myriad reasons, including the presence of other health conditions normally associated with aging, such as poor heart function and type II diabetes. Fortunately, outcomes for the elderly have significantly improved advances in surgery, radiotherapy, and palliative care, along with the advent of the molecularly targeted therapeutics era. However, a need still exists for effective methods of predicting therapeutic toxicities in the elderly, and recent research has made inroads in developing some models that could help in this regard (139). Undoubtedly, continued research will only further advance our ability to effectively treat our most at-risk populations.

A major concern for all cancer survivors is the return of their cancer or the development of a new cancer. Just as a healthy approach to living can prevent the development of cancer, it can also help prevent a cancer recurrence (see **Healthy Living Can Prevent Cancer From Developing, Progressing, or Recurring**, p. 14). For example, emerging evidence indicates that regular, intense aerobic exercise can reduce recurrence and mortality in early breast, prostate, and colorectal cancer survivors (140). However, adopting healthy approaches to living can be as difficult for cancer survivors as it is for otherwise healthy individuals. More research is necessary to understand how best to help modify behaviors to embrace healthy living approaches.

In addition to adopting healthy living approaches, some cancer patients receive treatment for a time after their initial therapy is complete to help decrease their risk for tumor recurrence and metastasis emergence, thereby increasing their chance of long-term survival. This approach is called adjuvant therapy, and it can be any form of anticancer therapeutic or radiotherapy.

Although the concept of adjuvant therapy is not new, it is becoming more common because many new anticancer therapeutics are better tolerated, although not completely without side effects. As a result, patients may be able to take them for longer periods. Whether a patient receives adjuvant therapy depends on a number of factors, including the stage of disease and other factors that may categorize a tumor as having a higher risk of recurrence. A clinician can prescribe adjuvant treatment for nearly any form of cancer; however, it is most commonly prescribed for high-risk forms of breast cancer, colorectal cancer, melanoma, and some gynecologic cancers.

Recent research has identified a potential new adjuvant therapy approach to decreasing tumor recurrence for patients with hormone receptor–positive breast cancer (141). Specifically, results from two large-scale clinical trials showed that inclusion of an antiestrogen therapeutic called exemestane, as part of a five-year course of adjuvant therapy, decreased cancer recurrence in premenopausal women with breast cancer fueled by estrogen (141).

Given that research has shown that about one in four cancer survivors has a decreased quality of life owing to physical problems and one in 10 owing to emotional problems (142), it is clear that much more research is needed to help the growing number of cancer survivors achieve a higher quality of life.

One issue that affects many women who survive cancer is infertility. Fortunately, a large-scale clinical trial recently reported promising results that may help preserve fertility for some of the 15 percent of premenopausal women diagnosed with breast cancer who have tumors that do not have hormone receptors or other molecules that can be targeted with precise therapeutics. The only therapeutics available to these patients are traditional chemotherapeutics, which frequently cause infertility by damaging the ovaries. In this clinical trial, women who were treated with a therapeutic called goserelin (Zoladex), which shuts down their ovaries, putting them into temporary menopause while they received chemotherapy, were almost twice as likely to have a normal pregnancy after their cancer treatment compared with women who did not receive goserelin (143).

These research advances provide new hope for premenopausal women who are cancer survivors. Unfortunately, these individuals form only a small proportion of the U.S. cancer survivor population and the advances address only some of the challenges faced by these patients. Further progress toward reducing the impact of cancer treatment on cancer survivors in the future will take a concerted effort from all stakeholders in the biomedical research community (see sidebar on **The Biomedical Research Community,** p. 2).

To address this need, a number of professional societies and not-for-profit organizations have recently developed clinical-practice guidelines that are designed to improve the prevention and management of some of the health-related issues affecting cancer survivors, including fatigue, anxiety and depression, and sexual dysfunction (144-146). Advocacy organizations, such as the Women Survivor Alliance, cofounded by **Karen Shayne** and **Judy Pearson** (see p. 78), also have an integral role to play if we are to meet the needs of cancer survivors, their loved ones, and future men, women, and children navigating the cancer journey.

WORKING TO PREVENT CHILDHOOD CANCER SINCE 2009

Cancer touches nearly every one of us in some way. My experience with the disease came at a very early age, when my best friend was diagnosed with leukemia in the fourth grade. At that time, survival rates for leukemia were not very promising. My friend ultimately passed away. It's one of those experiences you never forget as a kid—seeing your best friend battle and ultimately succumb to this terrifying disease. That has always stayed with me. Later, I lost my father to cancer, too.

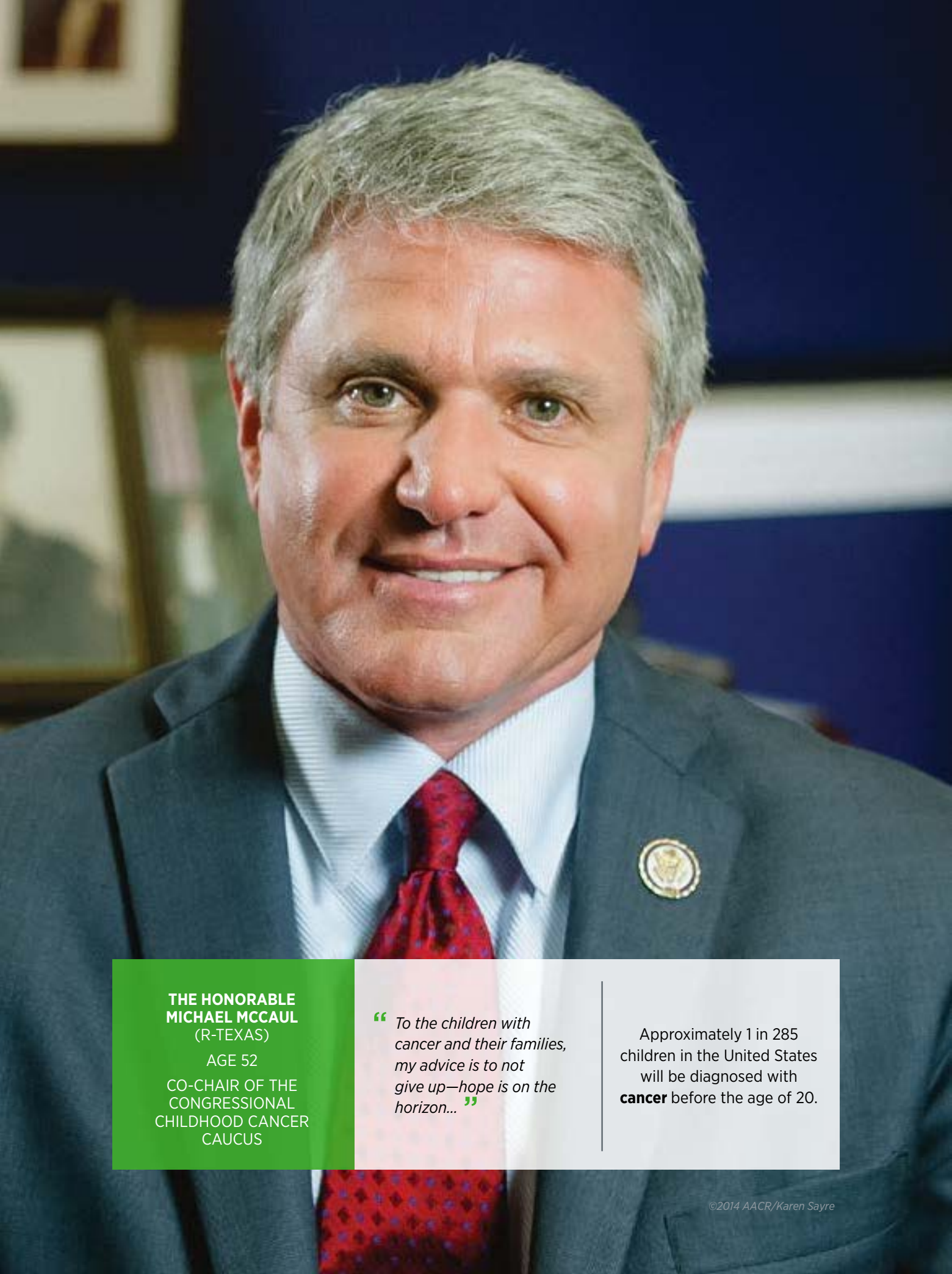
As a member of Congress, I have met numerous families who lost a child to cancer. Hearing their inspiring stories has deeply touched me, and through these conversations it became apparent to me that these children did not have strong advocates in the U.S. Congress. To give these children and their families a larger voice on Capitol Hill, I, along with former Congressman Joe Sestak (D-PA), formed the Congressional Childhood Cancer Caucus. Since 2009, the caucus has worked to advance the cause of preventing childhood cancer, the leading disease-related killer of our nation's children.

Co-chair Congressman Chris Van Hollen (D-MD) and I strive to increase awareness of childhood cancer, including the long-term and late effects of the disease, and to work toward the goal of eliminating cancer as a threat to all children. Each year, the caucus hosts a Childhood Cancer Summit on Capitol Hill. The event, now in its fourth year, is instrumental in raising the awareness level of members of Congress and staff about the unique and critical challenges facing childhood cancer survivors and their loved ones. It's also been a great opportunity for parents who have lost a child or have a child battling this disease to come together and call for increased funding and newer, more effective therapies.

Despite cancer claiming the lives of so many children, the tough reality is that only one drug has been approved by the FDA [U.S. Food and Drug Administration] for treatment of childhood cancer since the 1980s; this is unacceptable. There have been several efforts to address this in recent years that I am proud to have supported. The Caroline Price Walker Childhood Cancer Act, which passed unanimously, enhances research and identifies opportunities to expand the development of drugs necessary to treat the 13,500 children diagnosed with cancer in the United States every year. More recently, Congress worked hard to pass the Creating Hope Act, which, I think, will transform the way drug companies look at childhood cancer by providing incentives to create new therapies for the disease. It was really a special moment to be a member of Congress when we passed a bill that could make a difference in the lives of kids with cancer.

I am a strong supporter of the National Institutes of Health (NIH) because a strong investment in research is so important, particularly when it comes to childhood cancer, for which there's been a market failure. With every dollar invested in the NIH, over two dollars goes back into the economy. So not only is the NIH great for the nation's health, but it is also great for the economy and creates jobs. I recognize that we continue to operate under tight budget constraints, but funding the NIH must remain a strong priority of our nation.

I have deep admiration and respect for our nation's researchers who are on the frontlines in the fight against cancer. We must continue to invest in the biomedical research enterprise that is bringing hope to those afflicted by this disease. To children with cancer and their families, my advice is to not give up—hope is on the horizon—and to remember that Congress is more engaged and focused than ever on childhood cancer. I'm not just hopeful, but certain, that we will one day find a cure for this dreaded disease. At the end of the day, we all have to ask whether we're making a difference in the lives of others, and we have to empower others to be spokespersons and advocates for childhood cancer survivors and their families.



THE HONORABLE MICHAEL MCCAUL
(R-TEXAS)

AGE 52

CO-CHAIR OF THE CONGRESSIONAL CHILDHOOD CANCER CAUCUS

"To the children with cancer and their families, my advice is to not give up—hope is on the horizon..."

Approximately 1 in 285 children in the United States will be diagnosed with **cancer** before the age of 20.

©2014 AACR/Karen Sayre

WORKING TOGETHER TO HELP OTHER WOMEN NAVIGATE CANCER SURVIVORSHIP

Karen Shayne and Judy Pearson are very different people. Karen is in her mid-40s, a healthcare administrator from Nashville, Tennessee, with an outgoing personality, big hair, and boundless enthusiasm. Judy has just turned 60, a Michigan native who also lives in Chicago, and a writer of newspaper and magazine articles and books. Her favorite topic is the courage of ordinary people.

They lived in different worlds, many miles apart, but met because of one big thing they have in common: They are both cancer survivors. On their journeys, separate ones at first, they knew the fear and pain of dealing with cancer and the frustration that so often comes after, and they came together to make life better for others like them.

Karen was diagnosed with uterine cancer at the extraordinarily early age of 20. Already a college graduate and looking forward to starting a family, Karen fought the cancer for five years until her ovaries were involved and she had to have them removed, as well as undergoing a hysterectomy, followed by chemotherapy.

"All I thought about was, what is my life going to be like being childless?" she recalls. "As a newlywed, your heart just sinks, knowing that you brought a man into your life and you planned a life together, and now everything has changed."

She also found it difficult to reconcile her role in the healthcare industry with her status as a cancer patient.

"So I went into this hole. I didn't want to talk to people. I didn't want to deal with this. I wanted my journey to be quiet. I didn't even tell my mother until my hair started to fall out," she remembers.

Her doctors and caregivers focused on helping her beat the cancer, but when it was gone, she felt she was on her own. Even when she attended healthcare conferences that dealt with cancer, she heard little about the post-cancer experience.

She dealt with shock, then depression, then anger, and then, "Oh my God, what do I do now?" she says. "But I finally realized that we are all in this together, and that is what brought me out of the depression, and got me on a new and exciting journey."

Karen plunged into support and advocacy activities in the cancer community but felt the need for a greater focus on survivors, especially women. After talking it over with another survivor in 2009, she went home, pulled out a lipstick, and wrote on the mirror, "Survivors Convention." The idea took shape over time and moved closer to reality when Karen got a call from a persistent journalist from Chicago.

Judy's career as a writer had been suddenly interrupted in 2011 by a lump in her breast that a mammogram hadn't detected a few months before. "I am the poster child for how dense breast tissue can make breast cancer screening difficult," she says. A biopsy led to a diagnosis of triple-negative breast cancer, which was treated with a mastectomy and 18 rounds of chemotherapy.

"For me, the mastectomy was not frightening at all. But the chemo was terrifying," Judy says. "I lost my hair. I was really, really sick. But we all go through those things. What shocked me the most was that no one told me about the survivorship issues. No one told me I would have joint pain, fatigue, 'chemo brain,' night sweats three years later. That made me mad. I survived this horrible cancer, and I am still dragging this duffle bag of stuff behind me."

A great source of strength was the man she married just before having her cancer diagnosed.

"As a newlywed, I felt badly for my husband. I told him, this isn't what you signed up for. You don't have to stay. We could get it annulled. I don't know what I'm going to look like. I don't know if I'm going to live. You should probably go," she recalls.

"And he said to me, 'This is exactly what I signed up for, and I'm not going anywhere.' And there he was, an incredible rock, and together we kept trying to make sense out of all this."

Judy decided to write about her experience, and in 2012 her research led to Karen. The two became fast friends and sister survivors. Together they founded the Women Survivors Alliance, which held its first convention in 2013, with more than 800 in attendance from 49 states and five countries, and representing 27 forms of cancer.

The Women Survivors Alliance has three "ribbons" of support. The first is the convention, which is scheduled to be held in Nashville through 2015. Second, realizing the internet would give them the greatest reach, they launched a digital magazine called The Plum. A women's magazine, it covers nutrition, exercise, finance, skin care, and more, all with a focus on survivors.

Last, they created a platform called "My 2nd Act," giving women an opportunity to communicate how they're using their survivorship to help others. Read the essays and learn about the stage shows at www.survivorssecondact.com.

"Life changes dramatically after a cancer diagnosis," Judy says. "Survivorship is not a buzzword. It's a reality. You can never go back to being the person you were before the diagnosis. What we try to inspire women to realize is that the 'after' doesn't have to be a horrible, end-of-life stage. It can be as bright and beautiful and giving, and sometimes more valuable, than what you had before."

JUDY PEARSON
AGE 60
CHICAGO, ILLINOIS

“Life changes dramatically after a cancer diagnosis… You can never go back to being the person you were before the diagnosis… But the ‘after’ can be as bright and beautiful and giving, and sometimes more valuable, than what you had before.”

KAREN SHAYNE
AGE 47
NASHVILLE, TENNESSEE

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WHAT PROGRESS DOES THE FUTURE HOLD?

IN THIS SECTION YOU WILL LEARN:

- THE INCREASING USE OF GENOMICS AND COMPUTATIONAL BIOLOGY WILL SOON SPUR THE DEVELOPMENT OF MANY MORE ANTICANCER THERAPEUTICS AND NEW USES FOR OUR CURRENT TREATMENT ARSENAL.
- THROUGH RESEARCH SOME OF THE SIGNIFICANT CANCER HEALTH DISPARITIES THAT EXIST TODAY CAN BE ELIMINATED TOMORROW.

Unquestionably, advances in cancer research have spurred spectacular progress against cancer, with many more people living longer and leading fuller lives after a cancer diagnosis than ever before. Despite this progress, more than 1.6 million U.S. residents are projected to receive a cancer diagnosis and more than 585,000 are expected to die from the disease in 2014 alone (1). Therefore, it is imperative that we continue to use and explore all possible strategies for the prevention, detection, diagnosis, treatment, and cure of cancer if we are to make future lifesaving progress.

Fortunately, many researchers, like AACR President, 2014–2015, **Carlos L. Arteaga, MD** (see p. 82), think the future is bright. The explosion of new knowledge about cancer and the exciting technological advances, along with our ever-increasing understanding of how to apply them, will provide innovative ways to reduce the global burden of cancer.

Greater Deployment of Large-scale Genomics and Computational Biology

As discussed by Dr. Arteaga, technological advances in DNA sequencing have dramatically increased the number of known cancer-associated genomic alterations. This progress is anticipated to continue over the coming years, and it will multiply many times over the number of molecules that could provide a potential target for anticancer therapeutics.

To efficiently mine the enormous amounts of information generated by the genomic analyses of tumors and to identify the genomic alterations most likely to yield therapeutic targets with the potential to benefit patients, we will need to engage researchers in the fields of computational biology and bioinformatics. In fact, our ability to interpret all the information we collect to inform cancer care will be possible only by creating new storage infrastructure, educating the current and future workforce to understand the meaning of the data generated, and assembling teams of physicians and researchers from multiple disciplines, including nonbiological disciplines such as the physical, chemical, engineering, and mathematical sciences.

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 (147).

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 (147).

In addition to identifying the most promising therapeutic targets, computational biology and bioinformatics may help pinpoint the best combinations of therapeutics. Although molecularly targeted therapies have transformed the lives of many patients, the majority of tumors eventually develop resistance to these agents (see sidebar on **The Challenge of Treatment Resistance**, p. 57). As a way of starting to address this challenge, the FDA approved a combination of two molecularly targeted therapeutics for the same disease for the first time in January 2014 (see **Two Approaches to Address Treatment Resistance**, p. 56). This so-called rational combination of therapeutics, based on our understanding of cancer biology, is being tested in clinical trials as a way to overcome treatment resistance. Given that the number of potential combinations of molecularly targeted therapies is already immense, and will increase dramatically as the number of these cancer treatments rises in the future, continued progress will require investment in the power of computational biology and bioinformatics to help identify the most likely effective drug combinations.

Greater Effort to Reduce Cancer Health Disparities

Great strides have been made in cancer prevention, detection, diagnosis, treatment, and, in certain cases, cure. However, some groups of individuals in the United States—in particular, racial and ethnic minorities—experience notably higher incidence of some types of cancer than the general population and/or suffer significantly poorer treatment outcomes (see sidebar on **Racial and Ethnic Differences in Cancer Incidence and Mortality**, p. 84).

Cancer health disparities in cancer screening

The data are percentage of men and women up-to-date on screening in the United States during 2000–2010 (149).

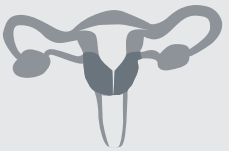
Breast cancer screening

White: 72%

African-American: 73%

American Indian/ Alaska Native: 69%

Asian: 64%



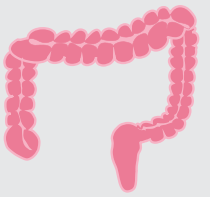
Cervical cancer screening

White: 83%

African-American: 85%

American Indian/Alaska Native: 79%

Asian: 75%



Colorectal cancer screening

White: 60%

African-American: 55%

American Indian/ Alaska Native: 50%

Asian: 47%

DR. CARLOS L. ARTEAGA, MD, AACR PRESIDENT, 2014–2015
ANTICIPATING MORE LIFESAVING PROGRESS IN THE FUTURE

During the 25 years that I have been a cancer investigator and oncologist, I have witnessed tremendous progress across the spectrum of cancer research, from bench to bedside, and I am supremely confident that we will continue to make rapid progress in the future.

When I first started my career as a physician scientist, our insight into the biology of cancer came mostly from studying mouse and human cancer cells in the laboratory. Now, increasingly, we interrogate tumors from patients, using the power of molecular biology to identify the molecular aberrations within them and then investigate these aberrations at the bench. This means that we have increasingly gone from a bench-to-bedside model of cancer research to one that is bidirectional.

The progress made in the laboratory has led to many of the changes that I have seen as an oncologist over the past two decades. One of the most recent advances has been an explosion in the use of predictive genomics for the interrogation of genetic alterations in tumors and, from that, making predictions about the biology of these cancers and how to treat them.

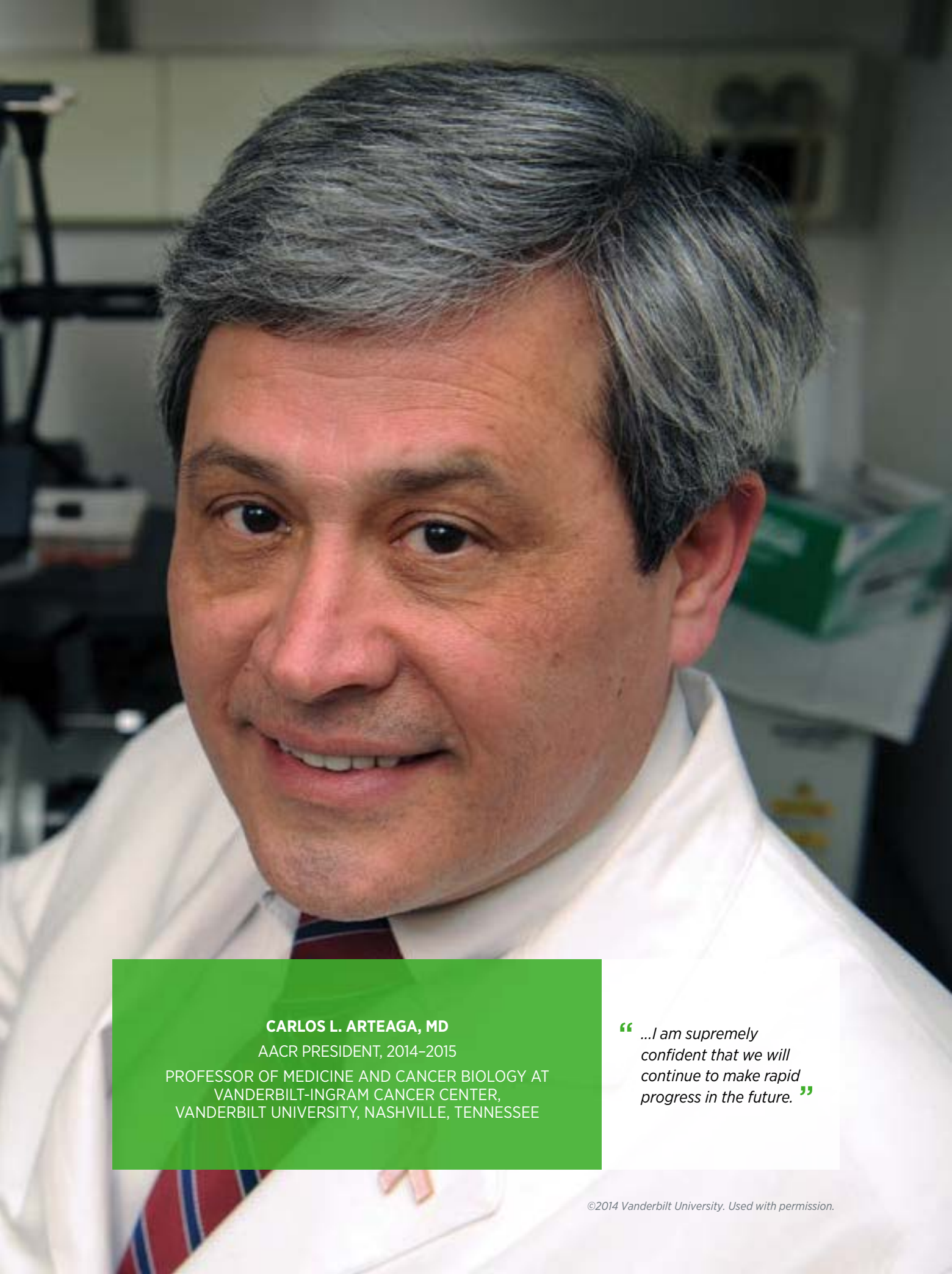
As we move forward, I foresee the increasing use of next-generation sequencing of tumors, which will allow us to dig more deeply into the biology of these cancers. This technology is advancing rapidly, and will allow us to examine more and more genes in a patient's cancer, and eventually the whole tumor genome. As we discover to what degree an increasing number of individual cancer-driving genes are altered in a tumor, the number of potential drug targets and drugs to block those targets should also increase. In addition, this approach will help us anticipate the behavior of a patient's tumor and identify mechanisms of acquired resistance to treatment that, in turn, can be trumped by novel therapies.

As we begin to identify more and more genetic alterations in a single tumor, we will need to use new ways to analyze our data. I think that the power of computational biology, which allows us to analyze many, many genetic alterations together, will revolutionize this area of cancer research.

One of the most important things we must do if we are to continue transforming lives is to better support our young investigators. We need to improve their training and do a much better job of recruiting them and retaining them in the field of cancer research. Some of the most transformative changes in cancer care have come from cancer research, which is driven by the innovative ideas of young and ambitious investigators. To me, addressing this issue is key to progress, and I will make it a priority during my presidency of the American Association for Cancer Research (AACR).

Another major challenge in cancer research is the crisis in federal funding, which sadly is occurring at a time in which the potential for progress has never been better. However, I am an optimist and would like to think that there are better times ahead. But we also need to further strengthen the alliance among patients, advocates, basic scientists, clinical investigators, and the private sector because I believe that support by the public will be crucial to resolving this funding crisis.

Despite all these hurdles, we are making significant progress on all fronts, at the bench and at the bedside. One thing that particularly excites me is that clinical trials have already become part of cancer care. Absolutely we could do more with greater funding and more young investigators, but the advances we have made mean that today in the United States, the majority of patients (more than 50 percent) survive their cancer. However, we owe it to those who don't survive to commit to continue working tirelessly. I anticipate that we will make more lifesaving progress in the future, and I am deeply committed to contributing to such progress.



CARLOS L. ARTEAGA, MD

AACR PRESIDENT, 2014–2015

PROFESSOR OF MEDICINE AND CANCER BIOLOGY AT VANDERBILT-INGRAM CANCER CENTER, VANDERBILT UNIVERSITY, NASHVILLE, TENNESSEE

“...I am supremely confident that we will continue to make rapid progress in the future.”

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RACIAL AND ETHNIC DIFFERENCES IN CANCER INCIDENCE AND MORTALITY

The likelihood that a person in the United States will develop a particular cancer or die as a result of it varies depending on their race or ethnicity. Some examples are highlighted here:

30% HIGHER	The cancer death rate among African-American men is 30 percent higher than among non-Hispanic white men, and for African-American women, it is 14 percent higher than among non-Hispanic white women (148).
34% HIGHER	The cancer death rate among Hispanic men is 34 percent lower than among non-Hispanic white men, and for Hispanic women, it is 35 percent lower than among non-Hispanic white women (13).
45% HIGHER	Compared with non-Hispanic white women, the breast cancer death rate among Hispanic women is 45 percent lower and is 36 percent higher among African-American women (109).
2X	Asian and Hispanic Americans are about twice as likely to develop and die from liver cancer as their white counterparts (148).
	People of Ashkenazi Jewish ancestry have an increased risk for several types of cancer, including breast, ovarian, pancreatic, and colorectal cancers.
	African-American men and women are significantly more likely to develop colorectal cancer and are almost twice as likely to die from it as their white counterparts (148).
MORE LIKELY	African-American men are more likely to develop prostate cancer than men of any other race or ethnicity and are more than twice as likely to die from the disease (148).
	American Indian/Alaska Native men are nearly twice as likely to develop and die from stomach cancer as non-Hispanic white men (148).
23% MORE LIKELY	Hispanic children are 23 percent more likely to develop leukemia than non-Hispanic children (13).

Among the many complex and interrelated causes of cancer health disparities are differences in access and use of cancer-screening programs (149). A number of initiatives have been developed and deployed to begin to address this aspect of cancer health disparities. One such initiative, which has been successful in eliminating colorectal cancer disparities, is the cancer control program that has been running in Delaware since 2003 (see sidebar on **Eliminating Colorectal Cancer Disparities in Delaware**) (150). Through this program, many patients from racial and ethnic minorities, including **Eleuterio Peguero Rosa** (see p. 86), have learned about and received colorectal cancer screening. Unfortunately, substantial financial, infrastructure, and social challenges may prevent the implementation of identical programs nationwide. As a result, other approaches to increasing colorectal cancer screening among currently underserved populations are being developed (151).

ELIMINATING COLORECTAL CANCER DISPARITIES IN DELAWARE

The cancer control program was initiated in 2003 under the direction of the Delaware Cancer Consortium (150). As a result of this program:

17% INCREASE	Colorectal cancer screening among all Delawareans age 50 or older rose from 57 percent in 2002 to 74 percent in 2009.
26% INCREASE	Colorectal cancer screening among African-Americans rose from 48 percent in 2002 to 74 percent in 2009, matching the 2009-screening rate among non-Hispanic whites.
ELIMINATED	Disparities in colorectal cancer incidence and mortality between non-Hispanic whites and African-Americans were eliminated as a result of the equivalent screening rates between the two groups.

BENEFITING FROM THE DELAWARE COLORECTAL CANCER SCREENING PROGRAM

I participated in the colorectal cancer screening program after learning about the importance of screening at a community center in my neighborhood. I had a precancerous polyp removed during my colon test [colonoscopy] and have benefited directly from this statewide effort.

I moved from the Dominican Republic in October 2011, just after I finished treatment for prostate cancer. Not long after I had been here, some doctors and nurses came to the community center in our neighborhood and talked about how everyone should have a test to look for colorectal cancer at age 50. They also gave out some pamphlets about the test and how we could get the test done if we were age 50 or older.

I hadn't known about having to get this test before I heard the doctors and nurses talk. After my prostate cancer diagnosis in early 2011, which was successfully treated with 35 rounds of radiotherapy, I had decided to look after my health and eat right. So, when I heard about the colon test I decided to make an appointment for it to safeguard my health.

During the test the doctors removed a polyp from my colon and they said that there might be something on the wall of my colon too. I thought I was going to have an operation a few months later but the doctors told me I didn't have colorectal cancer and that I didn't need an operation. Instead, they told me to come and have another colon test after a year.

I will be going for another colon test in October. I already have the list of things that I need to buy and things that I need to do to prepare for the test.

The doctors also told me what to eat to keep my colon healthy. I like to eat vegetables and fish. It is very important that you keep yourself healthy and eat right.

Through the program I was looked after very well. It is not so easy to get good medical care in the Dominican Republic and I am very thankful for the very good medical care I received here.

ELEUTERIO PEGUERO ROSA
AGE 71
WILMINGTON, DELAWARE

"I participated in the colorectal cancer screening program after learning about the importance of screening at a community center in my neighborhood."

The U.S. Preventive Services Task Force (USPSTF) recommends adults ages 50–75 be screened for **colorectal cancer** through fecal occult blood testing yearly, sigmoidoscopy every 5 years, or colonoscopy every 10 years.

2014 AACR/Vera LaMarche

A PRESCRIPTION FOR INCREASING THE RATE OF PROGRESS AGAINST CANCER

IN THIS SECTION YOU WILL LEARN:

- THAT TO INCREASE THE RATE OF PROGRESS AGAINST CANCER WE MUST SUSTAIN GROWTH IN FUNDING FOR BIOMEDICAL RESEARCH;
- DEVELOP THE WORKFORCE OF TOMORROW;
- ENHANCE PATIENT ENGAGEMENT AND AWARENESS;
- ADVANCE REGULATORY SCIENCE AND POLICY; AND
- PROMOTE EVIDENCE-BASED PREVENTION STRATEGIES.

The efforts of many thousands of basic, translational, and clinical researchers have led to a profound understanding of the genetic and molecular basis of the more than 200 diseases we collectively call cancer and has provided us with new and improved ways of preventing, detecting, diagnosing, treating, and, in some cases, curing these diseases. This progress would not have been possible without past investment in the NIH and NCI, which are charged with providing vital funding to and scientific oversight of the biomedical research community.

Although tremendous advances in our understanding of cancer have been made, there remains much that we do not yet know about the disease, underscoring the importance of making biomedical research a national priority again.

Prioritizing biomedical research will provide us with a more comprehensive understanding of the biology of cancer and its causes, and it will enable the translation of this knowledge into health care advances at a much more rapid rate than is happening today. Revitalizing investment in biomedical research will ensure that scientists have the funds they need to continue to make groundbreaking discoveries, and that early-career researchers will be more than adequately trained to meet the challenges ahead. It will also enable the development and expanded use of the novel research tools and technologies that are transforming science. With additional support for the NIH and NCI, we can be confident that extraordinary progress will be made against cancer for many years to come (see sidebar on **A Prescription for Increasing the Rate of Progress Against Cancer**).

A PRESCRIPTION FOR INCREASING THE RATE OF PROGRESS AGAINST CANCER

To increase the rate of progress against cancer we must:

sustain growth in funding for cancer research.

develop the workforce of tomorrow.

enhance patient engagement and awareness.

advance regulatory science and policy.

promote evidence-based prevention strategies.

Sustain Growth in Funding for Biomedical Research

During the past half century, bipartisan support from Congress and the administration for the NIH and NCI has enabled extraordinary progress against cancer. In doing so, it has saved countless lives, created jobs, and promoted economic growth in the United States. It has also catalyzed the development of the biotechnology industry and secured the United States position as the global leader in science and innovation. Therefore, if we are to increase the rate of progress we are making in the battle against cancer, while at the same time ensure that economic growth in the life sciences continues, it will require sustainable increases in federal funding for the NIH and NCI (see sidebar on **NIH: A Catalyst of Progress**).

NIH: A CATALYST OF PROGRESS

The funding for research provided by the NIH can lead to:

the discovery and development of new approaches for the prevention, detection, diagnosis, and treatment of cancer and other diseases;

improvements in the health of Americans and people around the world;

job creation and economic growth across the country; and

global leadership for the United States in the life sciences and biomedical research.

From Jan. 1, 2010, through July 31, 2014, we have realized remarkable returns on the federal government's prior investments in cancer research through the NIH and NCI. In fact, in those four and a half years, 39 new anticancer agents and 11 new uses for previously approved anticancer therapeutics have been FDA approved. In addition, this time period saw four new imaging technologies and FDA clearance for broad clinical use of a DNA sequencing machine and reagents.

For the NIH and NCI to have the resources required to build upon prior and current progress, biomedical research must once again become a national priority for our policymakers. Members of Congress must restore the $1.6 billion in NIH funding that was cut as a result of sequestration, and provide sustained funding increases at a rate that is at least comparable to biomedical inflation (see **Figure 14**, p. 90). In fact, NIH's current funding level is $3.5 billion less than where it would be today if it had simply grown at the same rate as biomedical inflation since 2010; this translates to a loss of more than $5 billion in purchasing power since that time.

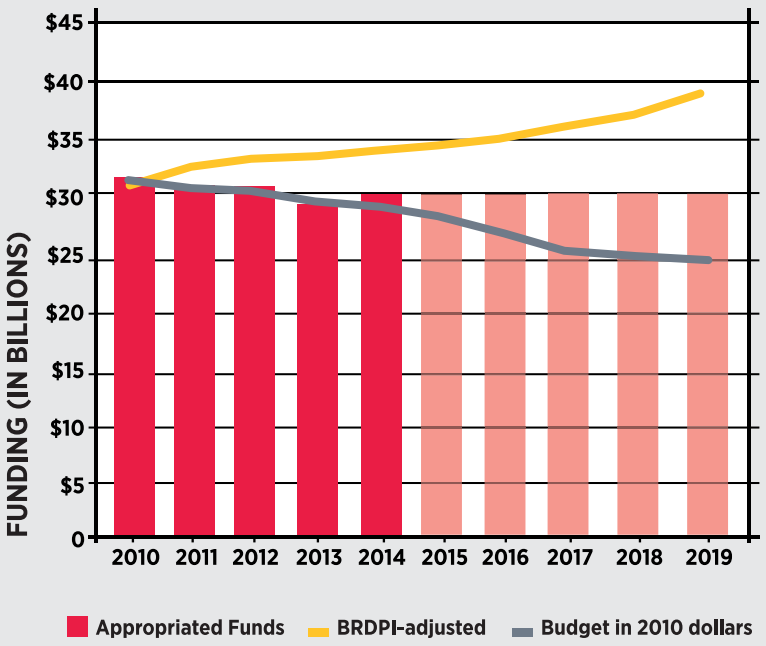
Develop and Retain the Workforce of Tomorrow

As a result of diminished federal support for biomedical research, a new research grant application to the NIH in 2013 had a less than one in six chance of receiving funding (152). Faced with an inability to sustain their research programs, some established NIH-funded investigators are leaving the field, which means that there are fewer opportunities for training. In addition, with fewer and smaller grants (153, 154), some established researchers are unable to take on new graduate students and postdoctoral scientists, and expert laboratory staff members have been let go. These cuts not only reduce the research capacity of our nation's laboratories but they also discourage promising trainees and early career scientists from even pursuing a career in cancer research, an outcome that has grave consequences for future innovation in the field. By adversely affecting the promise and progress in cancer research, these losses will unquestionably be detrimental to the lives of patients with cancer in the future.

In addition to allocating the funds necessary to recruit and retain the best and the brightest to the field of biomedical research, we must equip our workforce with the knowledge and skills to conduct state-of-the-art cancer research (see sidebar on **World Class Training**, p. 90). Cancer is a complex disease requiring multifaceted and interdisciplinary solutions. Further, an understanding of the advances in one field can have a profound effect on another. For example,

FIGURE 14 | **AT A CROSSROADS**

The Biomedical Research and Development Price Index (BRDPI) reflects the rising cost of personnel, supplies, and equipment needed to conduct biomedical research. The red bars indicate National Institutes of Health (NIH) budget levels, and the red transparent bars are an estimated budget based on 2014 levels. The gray line indicates that the current effective funding level for the NIH is $3.5 billion less than where it would have been today if it had simply grown at the same rate as BRDPI since 2010 (gold line). This discrepancy translates into a loss of more than $5 billion in purchasing power. Congress is faced with a choice. It can choose to make biomedical research a priority by funding the NIH at a level at least commensurate with BRDPI (gold line). If it chooses to fund biomedical research at the current rate, the budget of the NIH will continue along the red line, and patients will undoubtedly be affected. Thus, it is clear that there is only one viable path forward (gold line).



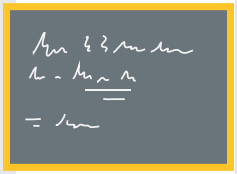
the development of cancer immunotherapies would not have been possible without basic research in immunology and without the new technologies that exist today. Likewise, drugs that were originally developed for cancer patients have led to treatments for macular degeneration, hepatitis, psoriasis, and other diseases.

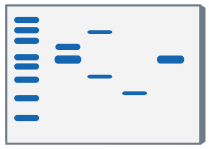
To capitalize on the full breadth of our research enterprise, both trainees and established investigators should be encouraged and have opportunities to engage with and learn from researchers across fields, including mathematics; engineering; and the physical, chemical, and social sciences.

WORLD CLASS TRAINING

To build the biomedical research workforce of the future we must provide:

training in basic, translational, and clinical research;	training in regulatory science;	access to cutting edge tools and techniques;	training in team science; and	professional development training.





Enhance Patient Education and Engagement

To obtain a deeper understanding of cancer and speed the development of new and improved cancer interventions, it is essential to engage patients throughout the continuum of research and care. Unfortunately, fewer than 5 percent of adult cancer patients participate in a clinical trial (155). Participation is even smaller among the elderly, women, racial and ethnic minorities, and people living in rural areas. To achieve outcomes relevant to all segments of the population, it is essential to increase the number and diversity of clinical research participants through a combination of outreach, education, and policy changes aimed at overcoming the barriers that prevent individuals from participating in these studies.

However, advancing patient-centered cancer research involves more than simply increasing the number and diversity of patients participating in research. Research policies should encourage the engagement of patients in the conception, design, and dissemination of research in order to address the questions that are most important to them, their loved ones, and their caregivers; help researchers to measure health outcomes from the perspectives of patients; minimize the barriers to patient participation; and ensure that research findings are shared with the patient communities that they are intended to benefit.

Jakafi (Ruxolitinib),

a drug used to treat myelofibrosis, was granted FDA approval based on novel endpoints, including the impact of the drug on symptoms reported by the patients (patient-reported outcomes).

Another way to advance patient-centered research is to better integrate laboratory and clinical data, making it possible for researchers to use data generated in the clinic to answer scientific questions and helping health care providers rapidly deliver care that is consistent with the latest research findings (see **Figure 8**, p. 33). To make this vision a reality, it will be important to facilitate the development of data infrastructure, standards, and policies that enable the capture, aggregation, analysis, and utilization of large volumes of high-quality clinical information while protecting the rights and privacy of the patient community.

Maximize Opportunities in Regulatory Science and Policy

Translating a deeper understanding of cancer biology into a new medical product benefitting cancer patients costs an average of about $1 billion, and the process can take over a decade (see **Clinical Trials**, p. 35). The growing field of regulatory science holds the key to improving efficiencies in this process.

Regulatory science is the study of developing new tools, standards, and approaches to assess the safety, efficacy, quality, and performance of medical products (see sidebar on **Regulatory Science**, p. 92) and is an integral part of FDA's review and decision-making processes. FDA's regulatory science initiatives are aimed at developing evidence-based regulatory policies and expediting development of more safe and effective medical products for cancer patients everywhere.

Thanks to the amazing progress made thus far against cancer, as highlighted in this document, the FDA is increasingly being asked to evaluate and regulate many novel therapies and technologies, such as immunotherapies and DNA sequencing. In many cases, the medical products under review are so novel that the current means of regulating them are inadequate. Thus, to continue or accelerate the current pace of progress against cancer, it is essential that advances in regulatory science parallel those in basic, translational, and clinical science.

To advance regulatory science, regulators must have the resources to support research that informs the regulatory process, as well as a sufficient budget to recruit, develop, and retain a highly qualified regulatory staff. Likewise, enhanced scientific exchange, cooperation, and collaboration among stakeholders from academia, industry, advocacy, and government are critical to advancing this field. Fostering meaningful exchange among these groups can be accomplished by ensuring that regulators are permitted to travel to national and international scientific meetings, where they can be kept abreast of the latest developments

in the field and interact with foremost scientific experts in an open, neutral venue. These exchanges will ensure that the best evidence is used to evaluate novel medical products and that advances in regulatory science are communicated to the entire biomedical research community to inform their work.

The FDA is ensuring that Americans have access to safe and effective medicines while encouraging the development of innovative cancer treatments in a timely fashion. Sustaining a strong and well-informed FDA, which is an active part of the biomedical research community, is necessary to continue making progress against cancer and deliver hope to patients and their loved ones everywhere.

REGULATORY SCIENCE

Regulatory science is the study of developing new tools, standards, and approaches to assess the safety, efficacy, quality, and performance of medical products, and it can help:

- determine toxicities of new therapeutics at an earlier stage in therapeutic development;
- determine optimal dosing strategies;
- design and implement more efficient clinical trials;
- develop novel tools and metrics to assess the safety and efficacy of new medical products more quickly (see **New Path to Approving Breast Cancer Therapeutics**, p. 64);
- leverage the power of new technologies, such as health information technology, to more efficiently evaluate new medical products;
- develop, evaluate, and regulate complex new medical products in a streamlined fashion; and
- evaluate the risks and benefits of new treatments in a more informed manner.

Adapted from: http://www.fda.gov/ScienceResearch/SpecialTopics/RegulatoryScience/default.htm?utm_campaign=Goo.

Promote Evidence-based Cancer Prevention Policies

Developing a better understanding of the numerous factors that contribute to cancer risk (see **Figure 4**, p. 15) will help researchers and policymakers to develop effective cancer prevention strategies. As noted earlier in this report (see **Healthy Living Can Prevent Cancer From Developing, Progressing, or Recurring**, p. 14), one of biggest success stories in cancer prevention is in the area of tobacco control. This progress was made possible through research demonstrating the adverse health consequences of smoking and through the implementation of policy and educational initiatives aimed at preventing tobacco use and encouraging cessation.

14 Tobacco Centers of Regulatory Science (TCORS)

were established in 2013 by the FDA and NIH to perform research to inform the regulation of tobacco products. The centers will investigate: diversity of tobacco products; reducing addiction; reducing toxicity and carcinogenicity; adverse health consequences; communications; marketing of tobacco products; and economics and policies.

To continue our progress against cancer, we must continue to prioritize cancer prevention research as an important area of focus and implement cancer prevention and control programs (see sidebar on **Eliminating Tobacco Use Faster**, p. 93). Comprehensive strategies for reducing cancer risk should include improvements in cancer risk assessment, screening methods, and other clinical interventions; public education and outreach regarding risk reduction; and the implementation and enforcement of social and economic policies aimed at promoting healthy behaviors.

Sunlamp products and ultraviolet (UV) lamps

were classified as moderate-risk (class II) devices by the FDA as of May 2014. Thus, all sunlamp products must now carry a visible warning stating that persons under the age of 18 should not use them, and marketing materials must include similar warning statements and contraindications.

ELIMINATING TOBACCO USE FASTER

The 2014 Surgeon General's report, "The Health Consequences of Smoking—50 Years of Progress," outlines the following strategies for eradicating tobacco use (18):

sustain high-impact anti-tobacco media campaigns for a prolonged period;

increase cigarette taxes;

provide access to proven tobacco use cessation treatments;

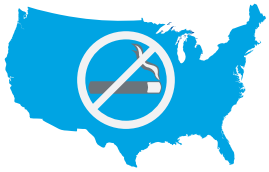
expand smoking cessation efforts for all smokers in primary and specialty care settings;

effectively implement the U.S. Food and Drug Administration's authority to regulate tobacco products;

increase tobacco control and prevention research efforts;

fully fund comprehensive statewide tobacco control programs at levels recommended by the Centers for Disease Control and Prevention; and

extend comprehensive smoke-free indoor protection to 100 percent of the U.S. population.



THE AACR CALL TO ACTION

IN THIS SECTION YOU WILL LEARN:

THAT THE AACR RESPECTFULLY URGES THE ADMINISTRATION AND CONGRESS TO PRIORITIZE THE GROWTH OF THE NIH AND NCI BUDGETS AT A PREDICTABLE, ROBUST PACE BY PROVIDING ANNUAL BUDGET INCREASES AT LEAST COMPARABLE TO THE BIOMEDICAL INFLATION RATE.

We are now at a crossroads in our country's long struggle to prevent and cure cancer; we must choose between two paths, but there is only one viable path forward to continue transforming lives.

On the viable path we seize the momentum at this exciting time in biomedical research by committing to budget increases for the NIH and NCI so that the remarkable progress of the past can continue at a rapid pace.

To take the alternative path is simply unacceptable. This particularly dangerous path leads us to a place where federal funding for biomedical research remains stagnant or, even worse, declines, seriously jeopardizing the rate at which we are able to make progress. On this path, breakthroughs and discoveries will be slowed, meaning that delivery of the cures that patients and their loved ones desperately need is delayed. Early-career researchers may be forced to leave science for other fields, further jeopardizing continued future progress.

The AACR respectfully urges Congress to do the right thing for cancer patients and our nation and choose the only viable path forward, which is to:

Prioritize the growth of the NIH and NCI budgets at a predictable, robust pace by providing annual budget increases at least comparable to the biomedical inflation rate.

Rededicating our country to the promise of biomedical research requires strong leadership from the administration and Congress. It also requires a commitment from all Americans to support federal funding for biomedical research and to communicate this view to policymakers.

As a country we must set priorities and make difficult choices at this fiscally challenging time in our history. Our federal government can do no better than invest robustly in the NIH and the NCI so that the path forward will lead us to a brighter future for the millions of people whose lives have been touched by cancer.

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GLOSSARY

Acute lymphocytic 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 lymphoblastic leukemia.

Adjuvant therapy Treatment given after completion of a patient's initial therapy to increase the chance of long-term survival. Adjuvant therapy may be chemotherapy, radiation therapy, hormone therapy, targeted therapy, and/or biological therapy.

Anaplastic large cell lymphoma (ALCL) A rare type of non-Hodgkin lymphoma, which usually arises from T cells (see T cell). The cells accumulate in the lymph nodes, skin, bones, soft tissues, lungs, or liver. In some cases, the anaplastic large cell lymphoma cells have the protein ALK (see Anaplastic lymphoma receptor tyrosine kinase) on their surface.

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 carcinomas (see Non–small cell lung carcinoma); some neuroblastomas; and some lymphomas, in particular, anaplastic large cell lymphomas (see Anaplastic large cell lymphoma).

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.

B cell A type of immune cell that makes proteins, called antibodies, which bind to microorganisms and other foreign substances, and help fight infections. A B cell is a type of white blood cell. Also called B lymphocyte.

Biomarker A biological molecule found in blood or other body fluids or tissues that is a sign of a normal or abnormal process, or of a condition or disease. A biomarker may be used to see how well the body responds to a treatment for a disease or condition. Also called molecular marker and signature molecule.

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

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.

Breast cancer Cancer that forms in tissues of the breast. The most common type of breast cancer is ductal carcinoma, which begins in the lining of the milk ducts (thin tubes that carry milk from the lobules of the breast to the nipple). Another type of breast cancer is lobular carcinoma, which begins in the lobules (milk glands) of the breast. Invasive breast cancer is breast cancer that has spread from where it began in the breast ducts or lobules to surrounding normal tissue. Breast cancer occurs in both men and women, although male breast cancer is rare.

Bruton tyrosine kinase (BTK) The BTK protein is generated from the BTK gene. It is found inside certain cell types—in particular, B cells (see B cell)—where it is involved in signaling pathways (see Signaling pathway/signaling network) that promote cell survival and multiplication. These signaling pathways are very important for survival of cancers arising in B cells, including chronic lymphocytic leukemia and mantle cell lymphoma (see Chronic lymphocytic leukemia and Mantle cell lymphoma, respectively).

Burkitt lymphoma An aggressive (fast-growing), rare type of non-Hodgkin lymphoma, which arises from B cells (see B cell). There are three clinical subtypes of Burkitt lymphoma. The type seen in the United States is a sporadic subtype that most frequently affects children. The endemic subtype associated with infection with Epstein-Barr virus is most common among children in Africa. Infection with human immunodeficiency virus (HIV) predisposes to a third Burkitt lymphoma subtype.

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.

GLOSSARY

CD20 The CD20 protein is found on the surface of nearly all B cells (see B cell). Its function is not well understood, but it is a good therapeutic target because it is found on the surface of the majority of non-Hodgkin lymphomas that arise from B cells.

Cervical cancer A term for a group of cancers that are named for the kinds of cells found in the cancer and by how they look under a microscope. 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 test [see 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 Part of a cell that contains genetic information. Except for sperm and eggs, all human cells contain 46 chromosomes.

Chronic lymphocytic leukemia (CLL) The most common type of leukemia diagnosed among adults in the United States. CLL arises in lymphocytes, most commonly B lymphocytes (see B cell), 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.

Cytokine A type of protein that has an effect on the immune system. Some cytokines stimulate the immune system and others slow it down. Cytokines are often produced by immune cells but can also be produced by nonimmune cells. They can also be made in the laboratory and used therapeutically.

Cytotoxic chemotherapy Anticancer drugs that kill rapidly dividing cells, including cancer cells.

Cytotoxic T lymphocyte antigen-4 (CTLA-4) A protein on the surface of immune cells called T cells (see T cell). When CTLA-4 attaches to certain proteins on other immune cells, it sends signals into the T cells to tell them to slow down and stop acting aggressively. Thus, CTLA-4 acts as an immune checkpoint protein.

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

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

Diffuse large B-cell lymphoma The most common type of non-Hodgkin lymphoma diagnosed among adults in the United States. Diffuse large B-cell lymphoma is an aggressive (fast-growing) disease that arises from B cells (see B cell), which accumulate in the lymph nodes, spleen, liver, bone marrow, or other organs.

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.

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, relief of symptoms, 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.

Gastric cancer Cancer that arises in cells lining the stomach. Cancers starting in different sections of the stomach may cause different symptoms and often have different outcomes. Infection with the bacterium Helicobacter pylori (see Helicobacter pylori) is a major cause of gastric cancer, except for gastric cancers arising in the top portion of the stomach, called the cardia.

Gastroesophageal junction adenocarcinoma Cancer that arises in cells located where the esophagus (the tube that connects the throat and stomach) joins the stomach. This gastroesophageal junction includes the top portion of the stomach, called the cardia.

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

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

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

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

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

HER2 (human epidermal growth factor receptor 2) A protein found on the surface of some cells that can initiate a variety of signaling pathways, causing the cells to proliferate. It is found at abnormally high levels on the surface of many types of cancer cells, including some breast cancer cells, so these cells may divide excessively. Also called ErbB2 and Neu.

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. Human papillomaviruses also play a role in some other types of cancer, including anal, oropharyngeal, penile, vaginal, and vulvar cancers.

Immune system A diffuse, complex network of interacting cells, cell products, and cell-forming tissues that protects the body from invading microorganisms and other foreign substances, destroys infected and malignant cells, and removes cellular debris. The immune system includes the thymus, spleen, lymph nodes and lymph tissue, stem cells, white blood cells, antibodies, and lymphokines.

Immunotherapy Treatment designed to produce immunity to a disease or enhance the resistance of the immune system to an active disease process, such as cancer.

Incidence The number of new cases of a disease diagnosed each year.

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 (system) The tissues and organs that produce, store, and carry white blood cells that fight infections and other diseases. This system includes the bone marrow, spleen, thymus, lymph nodes, and lymphatic vessels (a network of 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.

Magnetic resonance imaging (MRI) A noninvasive medical test that produces detailed pictures of areas inside the body through the use of radio waves and a powerful magnet linked to a computer. MRI is particularly useful for imaging the brain, spine, soft tissue of joints, and inside of bones. Also called nuclear magnetic resonance imaging (NMRI).

Mammography The use of film or a computer to create a picture of the breast.

Mantle cell lymphoma A form of non-Hodgkin lymphoma that arises in B cells (see B cell). The lymphoma cells accumulate in the lymph nodes, spleen, bone marrow, blood, and gastrointestinal system.

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.

Mutation Any change in the DNA of a cell. Mutations may be caused by mistakes during cell proliferation or by

exposure to DNA-damaging agents in the environment. Mutations can be harmful or 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.

Nanodrug A medicine composed of a therapeutic and a carrier that is less than 100 nanometers in size; for comparison, a sheet of paper is about 100,000 nanometers thick. For anticancer nanodrugs, the carrier is designed in such a way that it enhances delivery of the anticancer therapeutic to the cancer and protects the therapeutic from being destroyed by the body's defenses during transport.

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.

Neoadjuvant therapy Treatment given to shrink a patient's tumor prior to treatment that is intended to be curative, which usually includes surgery. Neoadjuvant therapy may be chemotherapy, radiation therapy, hormone therapy, targeted therapy, and/or biological therapy.

Non-Hodgkin lymphoma A term for a large group of cancers that arise in B cells or T cells (see B cell and T cell, respectively). Non-Hodgkin lymphomas can be aggressive (fast-growing) or indolent (slow-growing) types. B-cell non-Hodgkin lymphomas include Burkitt lymphoma, diffuse large B-cell lymphoma, and mantle cell lymphoma (see Burkitt lymphoma, Diffuse large B-cell lymphoma, and Mantle cell lymphoma, respectively). Anaplastic large cell lymphoma is one example of a T-cell non-Hodgkin lymphoma (see Anaplastic large cell lymphoma).

Non–small cell lung carcinoma (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 non–small cell lung cancer are squamous cell carcinoma, large cell carcinoma, and adenocarcinoma. Non–small cell lung cancer is the most common kind of lung cancer.

Oncogene A mutated (changed) form of a gene involved in normal cell growth. Oncogenes may cause the growth of cancer cells. Mutations in genes that become oncogenes can be inherited or can result from exposure to substances in the environment that cause cancer. The normal form of an oncogene is called a (proto)oncogene.

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.

Oral cancer The term given to a group of cancers that arise in cells of the mouth (the oral cavity) or the part of the throat at the back of the mouth (the oropharynx). The oral cavity includes the lips, the inside lining of the lips and cheeks, the gums, the front two-thirds of the tongue, the floor of the mouth below the tongue, and the bony roof of the mouth. The oropharynx is the part of the throat just behind the mouth (see Oropharyngeal cancer); it includes the back third of the tongue, the back part of the roof of the mouth, the tonsils, and the side and back walls of the throat.

Oropharyngeal cancer The term given to the subgroup of oral cancers (see Oral cancer) that arise in cells of the part of the throat at the back of the mouth (the oropharynx). The oropharynx includes the back third of the tongue, the back part of the roof of the mouth, the tonsils, and the side and back walls of the throat.

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.

Papanicolaou (Pap) test A test on a sample of cells taken from a woman's cervix. The test is used to look for changes in the cells that indicate cervical cancer or conditions that may develop into cancer. It is the best tool to detect precancerous conditions and hidden, small tumors that may ultimately develop into cervical cancer.

Pathologic complete response The absence of any detectable residual invasive cancer in a surgical specimen after presurgery (neoadjuvant) treatment (see Neoadjuvant therapy).

Peripheral T-cell lymphoma A term for a group of rare, aggressive (fast-growing) non-Hodgkin lymphomas that begin in mature T cells (see T cell). Anaplastic large cell lymphoma is one example of a peripheral T-cell lymphoma (see Anaplastic large cell lymphoma). Also called mature T-cell lymphoma.

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

Phosphatidylinositol 3-kinases (PI3Ks) A family of proteins that work inside cells to send signals that direct numerous cellular functions, including cell growth, proliferation, and survival. The gene that encodes one component of one PI3K is mutated, resulting in an inappropriately active protein in many types of cancer, including some breast cancers.

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

Prevalence The number or percent of people alive on a certain date in a population who previously had a diagnosis of the disease. It includes new (incidence) and pre-existing cases, and it is a function of both past incidence and survival.

Programmed death-1 (PD1) A protein on the surface of immune cells called T cells (see T cell). When PD1 attaches to programmed death ligand-1 (PDL1) on other immune cells, it sends signals into the T cells to tell them to slow down and stop acting aggressively. Thus, PD1 acts as an immune checkpoint protein.
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, like 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.

Sentinel lymph node the lymph node or lymph nodes to which a cancer is most likely to spread from the initial tumor. The presence or absence of cancer cells in these nodes helps determine the stage of disease.

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 activates 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.

Surrogate endpoint A direct measure, other than overall survival, of how a patient functions, feels, or survives that is used to determine when to stop a clinical trial. Surrogate endpoints are often used when the primary endpoint is undesired (e.g., death) or when the number of events is very small, thus making it impractical to conduct a clinical trial to gather a statistically significant number of endpoints.

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.

Therapeutic vaccine A type of therapy that uses a substance or group of substances to stimulate the immune system to destroy a tumor or infectious microorganisms, such as bacteria or viruses.

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 normal cells, molecules, and blood vessels that surround and feed a cancer cell. A cancer can change its microenvironment, and the microenvironment can affect how a tumor grows and spreads.

Tumor suppressor gene A type of gene that makes a protein called a tumor suppressor protein, which helps control cell growth. Mutations (changes in DNA) in tumor suppressor genes may lead to cancer. Also called antioncogene.

Uterine cancer Cancer that forms in cells of the uterus. There are two types of uterine cancer: endometrial cancer, which begins in cells lining the uterus; and uterine sarcoma, which arises in muscle or other cells of the uterus.

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.

Waldenström macroglobulinemia A rare, indolent (slow-growing) type of non-Hodgkin lymphoma that arises in B cells (see B cell). The lymphoma cells accumulate in the bone marrow, lymph nodes, and spleen. Also called lymphoplasmacytic lymphoma.

APPENDIX

SUPPLEMENTAL TABLE 1A | FDA-APPROVED CHEMICALS FOR THE TREATMENT OF CANCER

DNA SYNTHESIS INHIBITORS (ANTI-METABOLITES)

Approved Indication	Generic Name	Trade Name
Multiple cancers	5-fluorouracil (5FU)	Adrucil
Certain leukemias	6-mercaptopurine	Purinethol
Breast and colorectal cancers	capecitabine	Xeloda
Certain leukemias; lymphoma	cladribine	Litrak; Movectro
Certain leukemias	clofarabine	Clolar
Certain leukemias; lymphoma	cytarabine	DepoCyt; Cytosar-U
Stomach cancer	floxuridine	FUDR
Certain leukemias; lymphoma	fludarabine	Fludara
Pancreatic cancer	gemcitabine	Gemzar
Bladder, lung, and pancreatic cancers	gemcitibine	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
Prostate cancer	estramustine	Emcyt; Estracyt
Certain leukemias	idarubicin	Idamycin PFS
Multiple cancers	ifosfamide	Ifex
Colon, lung and rectal cancers	irinotecan	Camptosar; Campostar
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
Bladder cancer	valrubicin	Valstar

CELL CYTOSKELETON MODIFYING AGENTS

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

ANTI-NUTRIENTS

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

GENE TRANSCRIPTION MODIFIERS

Approved Indication	Generic Name	Trade Name
Certain lymphomas	bexarotene	Targretin
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

HORMONES/ANTI-HORMONES

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
Testicular and lung cancers	etoposide phosphate	Etopophos; Topusar; VePesid
Breast cancer	exemestane	Aromasin
Prostate cancer	flutamide	Eulexin
Metastatic breast cancer	fulvestrant	Faslodex
Prostate and breast cancers	goserelin acetate implant	Zoladex

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Breast cancer	letrozole	Femara
Prostate cancer	leuprolide acetate	Eligard; Lupron: Viadur
Breast and endometrial cancers	megestrol acetate	Megace; Megace Oral Suspension
Pituitary cancer	mitotane**	Lysodren
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
Myelodyspalstic syndrome; certain lymphomas	lenalidomide	Revlimid
Multiple myeloma	pomalidomide	Pomalyst

PROTEOSOME INHIBITOR

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

PROTEIN TRANSLATION INHIBITOR

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

EPIGENETIC MODIFIERS

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

ANGIOGENESIS INHIBITORS

Approved Indication	Generic Name	Trade Name
Kidney cancer	axitinib	Inlyta
Thyroid cancer	cabozantinib	Cometriq
Kidney cancer; soft tissue sarcomas; gastrointestinal stromal tumors	pazopanib	Votrient
Colorector 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

CELL SIGNALING INHIBITORS

Approved Indication	Generic Name	Trade Name
Certain type of lung cancer	afatinib	Gilotrif
Certain type of leukemia	bosutinib	Bosulif
Certain type of metastatic ALK-positive lung cancer	ceritinib†	Zykadia
Specific lung cancers*	crizotinib	Xalkori
Some leukemias	dasatinib	Sprycel
Certain type of melanoma*^	dabrafenib	Tafinlar
Some lung cancers*; pancreatic cancer	erlotinib	Tarceva
Some pancreatic cancers; kidney cancer; non-cancerous kidney tumors; HER2-, HR+ breast cancers	everolimus	Afinitor
Lung cancer	gefitinib	Iressa
Certain form of 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
Some leukemias	nilotinib	Tasigna
Certain types of leukemia	ponatinib	Iclusig
Myelofibrosis	ruxolitinib	Jakafi
Certain types of melanoma*^	trametinib	Mekinist
Kidney cancer	temsirolimus	Toricel; Torisel
Thyroid cancer	vandetanib	Caprelsa
Melanoma*	vemurafenib	Zelboraf
Certain type of skin cancer	vismodegib	Erivedge

INCREASING PRECISION

* includes companion diagnostic

** mechanism is not completely clear

^ first approval of a combination of targeted therapies for the same indication

† breakthrough therapy

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

APPENDIX

SUPPLEMENTAL TABLE 1B | FDA-APPROVED ANTICANCER MONOCLONAL ANTIBODIES

ANGIOGENESIS INHIBITOR

Approved Indication	Generic Name	Trade Name
Colon; kidney; and lung cancers	bevacizumab	Avastin
Certain types of stomach cancer	ramucirumab	Cyramza
Colorectal cancer	ziv-aflibercept**	Zaltrap

BLOOD CANCER SPECIFIC

Approved Indication	Generic Name	Trade Name
Certain leukemias	alemtuzumab	Campath
Certain lymphomas	brentuximab vedotin	Adcetris
Certain lymphomas	ibritumomab	Zevalin
Certain form of leukemia	obinutuzumab†	Gazyva
Certain leukemias	ofatumumab	Arzerra
Certain lymphomas	rituximab	Rituxan
Certain lymphomas	tositumomab I131	Bexxar

CELL SIGNALING INHIBITORS

Approved Indication	Generic Name	Trade Name
HER2+ breast cancer	ado-trastuzumab emtansine	Kadcyla
Colon cancer; head and neck cancer	cetuximab	Erbitux
Colon cancer	panitumumab	Vectibix
HER2+ breast cancer	pertuzumab	Perjeta
HER2+ breast cancer	trastuzumab	Herceptin

DIAGNOSTIC ANTIBODIES

Approved Indication	Generic Name	Trade Name
Imaging prostate cancer	capromab pendetide In111	Prostascint

IMMUNE STIMULATOR

Approved Indication	Generic Name	Trade Name
Melanoma	ipilimumab	Yervoy

METASTASIS INHIBITOR

Approved Indication	Generic Name	Trade Name
Bone metastases; certain bone cancer	denosumab	Xgeva

* includes companion diagnostic
** modified antibody
† breakthrough therapy

SUPPLEMENTAL TABLE 2 | SURGICAL AND RADIOTHERAPY ADVANCES

SURGICAL ADVANCES

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
Breast cancer, laryngeal cancer, and anal/rectal cancer	Neoadjuvant chemotherapy
Multiple cancers	Robotic or computer-assisted surgeries

RADIOTHERAPY ADVANCES

Used to Treat	Procedure
Prostate, cervical, other cancers	Brachytherapy
Multiple cancers	Image-guided radiation therapy (IGRT)
Multiple cancers	Intensity Modulated Radiation Therapy (IMRT)
Brain metastases	Stereotactic radiosurgery
Liver and lung cancers	Stereotactic body radiation therapy
Multiple cancers	Neoadjuvant and adjuvant radiotherapy combined with radiation therapy
Head and neck cancers	Radiation therapy combined with molecularly targeted therapy (cetuximab)
Prostate cancer	Radiation therapy combined with androgen deprivation
Prostate cancer	Adjuvant radiotherapy
Pediatric cancers	Proton Therapy
Unresectable glioblastoma, lung cancer, head and neck cancer, esophagus cancer, pancreas 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

AACR American Association for Cancer Research

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