

Special Feature on  
**Immunotherapy**

# AACR Cancer **Progress** Report **2013**

*Making Research Count for Patients: A Continual Pursuit*



**AACR** *American Association  
for Cancer Research*

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AACR Cancer **Progress** Report  
**2013**

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# A Message from the AACR



Sawyers



Foti

On April 8, 2013, in an unprecedented effort to highlight the critical importance of biomedical research, the American Association for Cancer Research (AACR) joined with more than 200 organizations representing a broad spectrum of research interests and diseases to “Rally for Medical Research” in our nation’s capital. This historic event, which united research advocates across the country and attracted more than 10,000 supporters to Washington, D.C., served as a call to action to raise awareness about the need to increase investments in the National Institutes of Health (NIH) to spur more progress, inspire more hope, and save more lives. The *AACR Cancer Progress Report 2013* echoes this rally cry by outlining why funding for the NIH and the National Cancer Institute (NCI) must be a national priority.

The report details how scientific discoveries propelled by federal investments in basic, translational, and clinical research are transforming cancer care and bringing hope to patients and their loved ones everywhere. These discoveries have led to decreases in the incidence of many of the more than 200 types of cancer, cures for a number of these diseases, and higher quality and longer lives for many individuals whose cancers cannot yet be prevented or cured.

Herein, this report focuses on the remarkable progress that has been made against cancer, and highlights how advances in one field can have a profound effect on others. For example, promising new therapies that harness the power of a patient’s immune system to treat their cancer would not have been realized without basic research in immunology. These types of therapies are described within a special feature in this report. Cancer research also impacts other diseases. Indeed, drugs originally developed for cancer patients have led to treatments for macular degeneration, atherosclerosis, psoriasis, rheumatoid arthritis, and hepatitis among others. The synergistic relationships among different research fields — and the relationships between certain diseases — underscore why it is so important for scientists, patients, and advocates across the spectrums of research and disease to join together in advocating for sustainable research funding.

This report and the ongoing community-wide effort to rally support for biomedical research could not come at a more important time. Cancer research and biomedical science

are facing the most serious funding crisis in decades. Since 2003, the budgets for the NIH and the NCI have been steadily shrinking because the amount of funding provided to them by Congress each year has been significantly less than what is needed to just keep pace with biomedical inflation. As a result, there has been an effective 20 percent reduction in the ability of these agencies to support lifesaving research. In addition to the gradual erosion of funding due to inflation, the NIH was forced to absorb \$1.6 billion in direct budget cuts in March 2013, under what is known as sequestration. The NCI suffered a commensurate budget cut of \$293 million. As a result, the NIH is now funding the lowest number of research projects since 2001, and unless Congress takes action, sequestration will result in an overall reduction to the NIH budget of \$19 billion by 2021.

The current course is simply unacceptable, and Congress must intervene, because the eroding support for cancer research has far-reaching negative implications. For example, shrinking budgets will adversely impact the ability of scientists to carry out ongoing research projects; reduce the number of promising new grant proposals that the NCI can support; diminish the funding available to cancer centers where critical “bench-to-bedside” research and care take place; and slow the progress of clinical trials, which will have a devastating effect on patients who will be forced to endure a delay in the development of new and improved treatments for their diseases.

What is worse is the fact that diminished federal investments in cancer research come at a time when the American people most need new research advances. Cancer is the second most common cause of disease-related death in the United States, exceeded only by heart disease, and it will become the number one killer in the very near future unless we are able to avert this projected increase in cancer cases through research. Cancer currently accounts for nearly one of every four disease-related deaths in the United States, and is expected to claim the lives of 580,350 Americans this year. In addition, it is estimated that 1.6 million Americans will be diagnosed with cancer this year. Globally, cancer incidence is also on the rise, and it is anticipated to claim the lives of approximately 13 million people by 2030.

## About the American Association for Cancer Research

Despite this sobering reality, federal policymakers can put biomedical research back on course. To do so, however, they must designate the NIH and NCI as national priorities and provide these vitally important institutions with sustained funding increases that are at least comparable to the biomedical inflation rate. In addition, Congress must take action to protect the agencies from sequestration, and to reinstate the \$1.6 billion in funding that the NIH lost in March 2013. The AACR also calls upon its members, and indeed all Americans — the beneficiaries of this lifesaving research — to make their voices heard by contacting their representatives and senators in Congress and urging them to vigorously support budget increases for the NIH and NCI. If policymakers fail to act, our ability to transform cancer care for the benefit of current and future cancer patients will be seriously compromised, and the crucial investments we have already made in biomedical research will be jeopardized.

The inspiring personal stories of the cancer survivors in this report are a testament to the value and importance of the biomedical research that is supported by the NIH and NCI. The AACR is deeply grateful to these courageous survivors for both their participation and willingness to share their stories. We stand with them and with patients and their loved ones everywhere in calling upon our policymakers to make every possible effort to help eradicate cancer. We ask you to join us in this quest to conquer cancer.

**Charles L. Sawyers, M.D.**  
AACR President

**Margaret Foti, Ph.D., M.D. (h.c.)**  
Chief Executive Officer

The mission of the American Association for Cancer Research (AACR) is to prevent and cure cancer through research, education, communication, and collaboration. Founded in 1907, the AACR is the world's oldest and largest scientific organization dedicated to advancing cancer research for the benefit of cancer patients.

Its membership includes 34,000 laboratory, translational, and clinical researchers who are working on every aspect of cancer research; other health care professionals; and cancer survivors and patient advocates in the United States and more than 90 countries outside the U.S. The AACR marshals the full spectrum of expertise from the cancer community to accelerate progress in the prevention, etiology, early detection, diagnosis, and treatment of cancer through innovative scientific and educational programs and publications. It funds innovative, meritorious research grants to both senior and junior researchers, research fellowships for scholars-in-training, and career development awards.

The AACR Annual Meeting attracts over 18,000 participants who share the latest discoveries and new ideas in the field. Special Conferences throughout the year present novel data across a wide variety of topics in cancer research, ranging from the laboratory to the clinic to the population. The AACR publishes eight major peer-reviewed journals: *Cancer Discovery*; *Cancer Research*; *Clinical Cancer Research*; *Molecular Cancer Therapeutics*; *Molecular Cancer Research*; *Cancer Epidemiology, Biomarkers & Prevention*; *Cancer Prevention Research*; and *Cancer Immunology Research*. In 2012, the AACR's scientific journals received 20 percent of the total number of literature citations in oncology.

The AACR also publishes a magazine, *Cancer Today*, for cancer patients, survivors, patient advocates, and their families and caregivers that includes essential, evidence-based information and perspectives on progress in cancer research, survivorship, and healthy lifestyle.

A major goal of the AACR is to educate the general public and policymakers about the value of cancer research in improving public health, the vital importance of increases in sustained funding for cancer research, and the need for national policies that foster innovation and progress in the field.

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# Executive Summary

## Background

Amazing progress has been made against cancer because of the dedicated work of researchers throughout the biomedical research enterprise. Their efforts have spurred, and continue to spur, the translation of scientific discoveries into new and better ways to prevent, detect, diagnose, and treat cancer. These remarkable advances are contributing to the rise in the number of people who are surviving longer and living life to the fullest after their cancer diagnosis. In fact, the number of cancer survivors living today in the United States is estimated to be more than 13.7 million.

The improvements in health care that have significantly reduced the burden of cancer were made possible by the scientific foundation provided through the many decades of investments in basic, translational, and clinical research. These investments come from the federal government, philanthropic individuals and organizations, and the private sector. The federal investments in biomedical research, made primarily through the National Institutes of Health (NIH) and the National Cancer Institute (NCI), have been particularly instrumental in building our current scientific foundation.

Although extraordinary advances in cancer research have deepened our understanding of how cancer develops, grows, and threatens the lives of millions, it is projected that 580,350 Americans will die from one of the more than 200 types of cancer in 2013. Moreover, because more than 75 percent of cancer diagnoses occur in those aged 55 and older and this segment of the population is increasing in size, we face a future where the number of cancer-related deaths will increase dramatically. As a result, cancer is predicted to soon become the number one disease-related killer of Americans. This trend is being mirrored globally, and it is estimated that in 2030, more than 13 million people worldwide will lose their lives to cancer.

As the number of cancer deaths increases, the economic burden of cancer will mushroom. Given that the global economic toll of cancer already is 20 percent higher than that from any other major disease, it is imperative that all sectors of the biomedical research enterprise work together to deliver future breakthroughs to help reduce the incidence of cancer.

Fortunately, we have never been better positioned to capitalize on our hard-won understanding of cancer — what causes it, what drives it. We now know that changes in an individual's genes alter certain protein components of the cell, driving cancer initiation, development, and spread (metastasis). We also know that therapies that specifically target these defects are often beneficial to patients while being less toxic than older therapies.

However, continued progress is in jeopardy. This is because investments in the NIH by the federal government have been steadily declining for the past decade. On top of this, on March 1, 2013, sequestration slashed the NIH budget by \$1.6 billion, or 5.1 percent.

This third AACR Cancer Progress Report to Congress and the American public seeks again to serve as a comprehensive educational tool that illustrates the astounding return on investment in cancer research and biomedical science, while also celebrating the many ways that we have continued to make research count for patients in the past year. Scientific momentum has brought the arrival of a new era in which we will be able to develop even more effective interventions and save more lives from cancer, but to do so will require an unwavering, bipartisan commitment from Congress and the administration to invest in our country's remarkably productive biomedical research enterprise.

## Prevention and Early Detection

Many of the greatest reductions in the morbidity and mortality of cancer have resulted from advances in cancer prevention and early detection.

Yet, more than 50 percent of the 580,350 cancer deaths expected to occur in the United States in 2013 will be related to preventable causes. Most notable among these causes are tobacco use, obesity, poor diet, lack of physical activity, exposure to ultraviolet radiation either through the use of tanning devices or direct sun exposure, and failure to use or comply with interventions that treat or prevent infectious causes of cancer. Modifying personal behaviors to adopt a healthier lifestyle that eliminates or reduces these risks,

where possible, could therefore, have a remarkable impact on our nation's burden of cancer. However, a great deal more research and resources are needed to understand how to best help individuals to change their lifestyle.

Finding a cancer early makes it more likely that it can be treated successfully. Thus, population-based screening programs have been implemented to detect a variety of cancers. Such programs have been credited with dramatically increasing the five-year survival rates for the cancers they detect; however, there is growing concern that this heightened surveillance leads to the overdiagnosis and overtreatment of some forms of cancer, and that it can do more harm than good.

One way to reduce overdiagnosis and overtreatment is to target screening programs to those individuals at highest risk for developing the cancers being detected. Therefore, continued research is needed to develop more concrete ways to identify the most at-risk patients, and more and better ways to intervene earlier in the progression of cancer.

## Making Research Count for Patients: A Continual Pursuit

Decades of cancer research have deepened our understanding of cancer biology. Exploiting this knowledge to make research count for patients is a continual pursuit that fuels the extraordinary medical and technical advances that are not only helping save millions of lives in the United States and worldwide, but are also improving the quality of lives.

From Sept. 1, 2012, to July 31, 2013, the translation of scientific discoveries into a new drug, device, or technique approved by the U.S. Food and Drug Administration (FDA) was completed for 11 new anticancer drugs, three new uses for previously approved anticancer drugs, and three new imaging technologies that are helping clinicians to better detect, diagnose, and treat many forms of cancer.

There are also many cancer therapeutics showing great potential in clinical trials. One group of cancer therapeutics likely to revolutionize the treatment of certain cancers in the very near future are immunotherapies. These therapeutics,

which train a patient's immune system to destroy their cancer, are yielding both remarkable and long-lasting responses. Moreover, not all immunotherapies work in the same way, and early studies indicate that combining immunotherapies that operate differently or combining immunotherapies with either radiation therapy or other drugs can enhance the benefits of these incredibly powerful anticancer therapeutics.

As a result of cancer genomics research, two of the new anticancer drugs approved by the FDA in 2013 were approved together with companion diagnostics to ensure that only patients who are likely to benefit from the drug receive it. This is an example of how large-scale genomic analysis of patients' tumors is beginning to guide cancer diagnosis and treatment. Further innovation is needed, however, if genetic/genomic analysis is to become part of standard clinical practice, and if most cancer treatment and prevention strategies are to be based on both a person's genetic makeup and the genetic makeup of their specific cancer.

## What is Required for Continued Progress Against Cancer?

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, both in the United States and throughout the world, while catalyzing the development of the biotechnology industry and promoting economic growth in America. However, there are many challenges to overcome if we are to realize our goal of conquering cancer.

First and foremost, if we are to accelerate progress toward our goal, we must continue to pursue a comprehensive understanding of the biology of cancer. This will only be possible if we make funding for cancer research and biomedical science a national priority. This includes investing in the talent, tools, and infrastructure that drive innovation, as well as advancing policies that enable researchers to more completely understand the complexities of cancer and to translate that knowledge for the benefit of patients.

Innovative efforts to develop new tools, new analytics, new ways of thinking, and new ways of working together will help researchers and their partners in the biomedical research enterprise forge ahead to the finish line — to the day when cancer is removed as a major threat to our nation's citizens and to future generations. Realizing this bright future requires that Congress, the administration, and the general public stand firm in their commitment to the conquest of cancer.

## The AACR Call to Action

To fulfill the extraordinary scientific and medical promise of cancer research and biomedical science, the AACR respectfully urges Congress to:

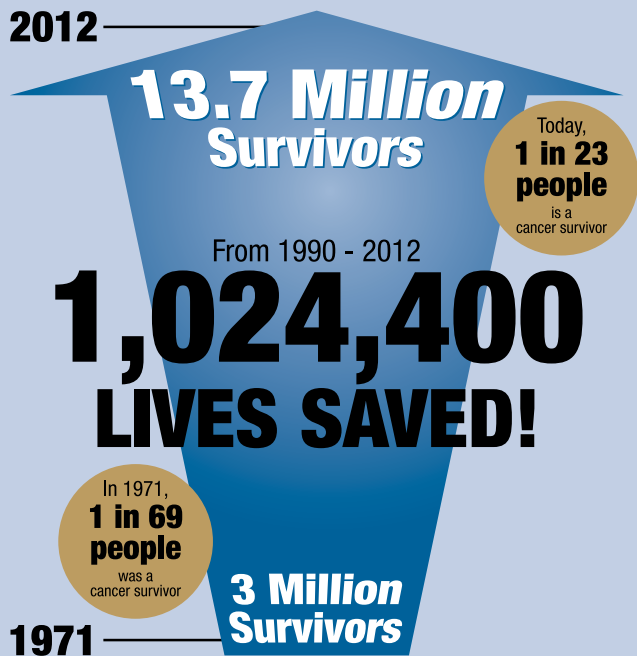
- Designate the NIH and NCI as national priorities by providing annual budget increases at least comparable to the biomedical inflation rate.
- Protect the NIH and NCI from another year of the insidious budget cuts from sequestration, and reinstate the \$1.6 billion in funding that the NIH lost in March 2013.

Therefore, the AACR calls on all Members of Congress to ensure that funding for cancer research and biomedical science is strongly supported. The AACR also urges all Americans — the beneficiaries of this lifesaving research — to make their voices heard by encouraging their policymakers to provide sustainable increases for the NIH.

If we are to ultimately transform scientific discoveries into therapies that improve and save the lives of cancer patients, it is going to require an unwavering commitment of Congress and the administration to invest in our country's remarkably productive biomedical research enterprise led by the NIH and NCI.

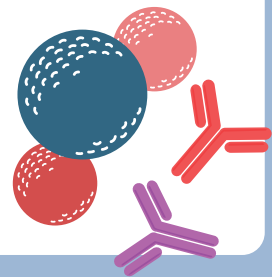
# A Snapshot of a Year of Progress

## Thanks to Cancer Research:



Fundamental discoveries in **immunology** are yielding remarkable and long-lasting patient responses through:

- 2 FDA-approved immunotherapies
- Numerous other immunotherapies currently in clinical testing



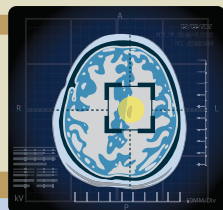
From Sept. 1, 2012 - July 31, 2013,  
The FDA has approved:

**11 new drugs** to treat a variety of cancers



**3 new uses** for previously approved anticancer drugs

**3 new imaging technologies**

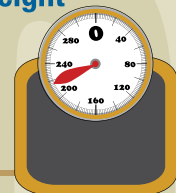


We know that more than **50%** of cancer deaths are related to **preventable** causes:

**Tobacco use**



**Obesity and being overweight**



**Lack of physical activity**



**Diet poor in nutrition**



# The Status of Cancer in 2013

## In this section you will learn:

- There are an estimated **13.7 million** cancer survivors in the United States.
- More than **1.6 million** Americans are projected to receive a cancer diagnosis in 2013 and more than **580,350** are expected to die of the disease.
- Global cancer incidence is predicted to increase from **12.8 million** new cases in 2008 to **22.2 million** in 2030.
- Cancer is the **most costly disease** to our nation.

**1,024,400**

There have been **1,024,400** fewer cancer deaths since 1990 and 1991 for men and women, respectively, as a result of declining death rates (4).

## The NIH

is 27 Institutes and Centers; funds 6,000 in-house scientists and 50,000 external grants annually; enables the work of more than 432,000 extramural researchers at more than 3,000 universities, medical centers, teaching hospitals, small businesses, and research institutions; and creates jobs in every state and around the world.

## Definitive Progress has Been Made Against Cancer

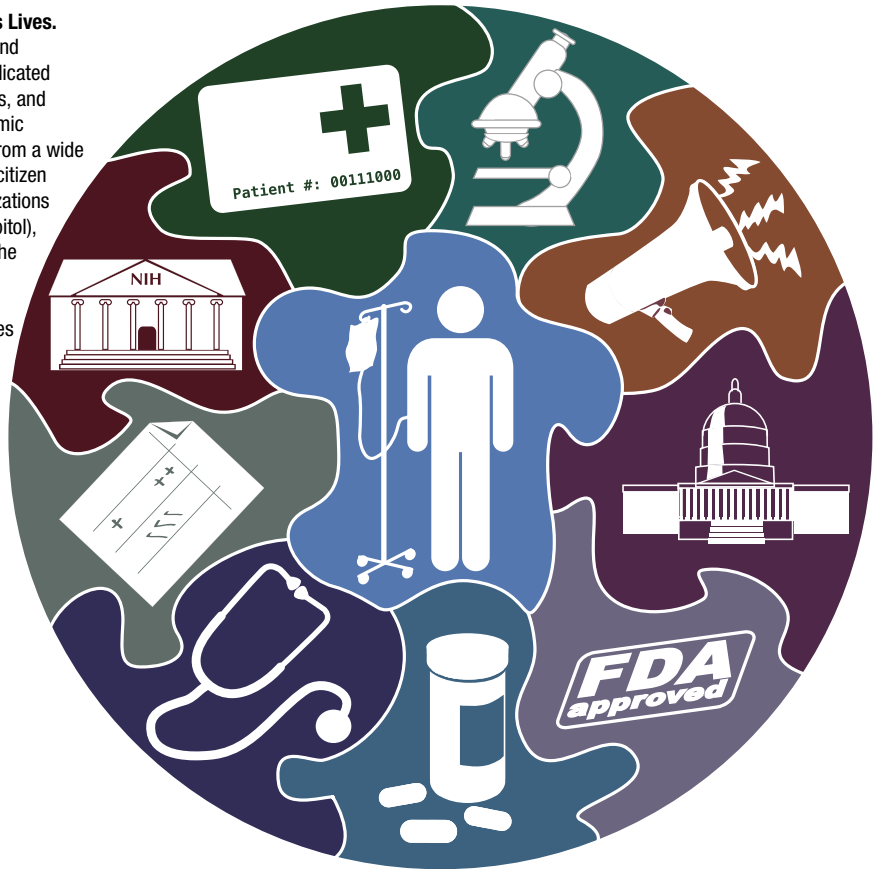
Significant progress has been and continues to be made against cancer. This progress is the result of dedicated efforts across all sectors of the biomedical research enterprise to increasingly translate basic scientific discoveries about cancer into new and better ways to prevent, detect, diagnose, and treat this disease (see **Figure 1**, p. 3). Indeed, in just 11 of the 12 months since the *AACR Cancer Progress Report 2012* (Sept. 1, 2012, to July 31, 2013), the U.S. Food and Drug Administration (FDA) approved 11 new drugs for treating cancers, three new uses for previously approved anticancer drugs, and three new imaging technologies (see **Table 1**, p. 4).

Due in part to advances like these, more people survive their cancers today than in the past (see **Figure 2**, p. 5). The National Cancer Institute (NCI) estimates that approximately 13.7 million Americans with a history of cancer were alive on Jan. 1, 2012 (1). This is almost 2 million more than its previous estimate of nearly 12 million in 2008 (2), and more than 10 million more than in 1971, the year the U.S. Congress passed the National Cancer Act (3).

The progress has been spurred by many decades of investments in basic, translational, and clinical research by the federal government, philanthropic individuals and organizations, and the private sector. Of particular importance are the investments in basic research supported by public funds through the National Institutes of Health (NIH) and NCI. Together, investments in biomedical research from all sectors have led to decreases in incidence for many of the more than 200 diseases we call cancer; cures for some of these diseases; and higher quality and longer lives for many individuals whose cancers cannot yet be prevented or cured.

**Figure 1: Working Together Saves Lives.**

Progress against cancer has been and continues to be the result of the dedicated efforts of many individuals, agencies, and organizations. These include academic scientists and clinical researchers from a wide variety of specialties (microscope), citizen advocates and philanthropic organizations (megaphone), government (U.S. Capitol), regulatory agencies (FDA symbol), the biotechnology and pharmaceutical industries (pills), physicians (stethoscope), diagnostics companies (notepad), funding agencies and philanthropic organizations (National Institutes of Health building), and payers (health insurance card). Central to transformative advances against cancer are the patients and survivors themselves.



## Even in the Face of Progress, Cancer Remains a Significant Problem

Unfortunately, advances have not been uniform for all types of cancer (see **Table 2**, p. 6). The five-year survival rates for some cancers, such as the most aggressive form of brain cancer (glioblastoma multiforme), and pancreatic, liver, and lung cancers, have not improved significantly over the past four-plus decades and remain very low, at 4 percent, 6 percent, 14 percent, and 16 percent, respectively (1, 4). In contrast, the five-year survival rates for women diagnosed with invasive breast cancer and for children diagnosed with acute lymphocytic leukemia have increased from 75 percent and 58 percent, respectively, to 90 percent or more since the mid-1970s (1). Moreover, advances have not been identical for all patients with a certain type of cancer, nor is the burden of cancer distributed evenly across the population, due to numerous interrelated factors.

Despite significant improvements in survival from many cancers, it is estimated that 580,350 Americans will die from some form of cancer in 2013 (1). Cancer will account for nearly one in every four deaths, making it the second most common cause of disease-related death in the United States. Unless more effective preventive interventions, early detection tools, and treatments can be developed, it will not be long before cancer is the leading cause of death for all Americans, as it already is among the U.S. Hispanic population (5).

## 1 out of 2

Almost one out of every two people born today will be diagnosed with cancer (1).

1/3

One-third of cancer deaths are caused by tobacco use (1).

1/3

One-third of cancer diagnoses are related to patients being overweight or obese, physically inactive, and consuming a diet poor in nutritional value (1).

**Table 1: Newly FDA-approved Drugs, Indications, and Technologies for the Treatment and Imaging of Cancer: Sept. 1, 2012-July 31, 2013**

**New Drugs**

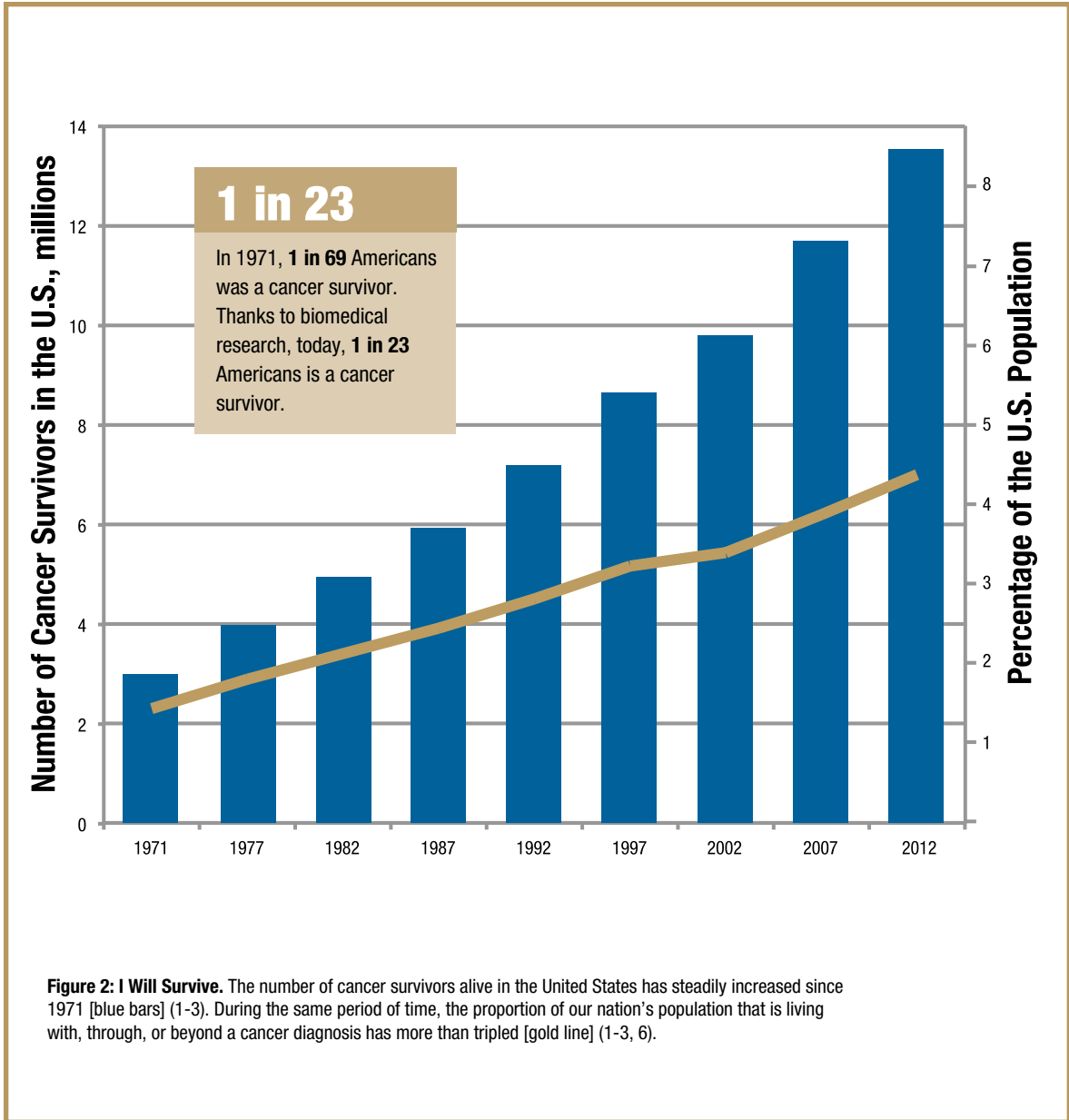
Angiogenesis Inhibitors			
Approved Indication	Generic Name	Trade Name	Formulation
thyroid cancer	cabozantinib	Cometriq	
colorectal cancer; gastrointestinal stromal tumors	regorafenib	Stivarga	
Cell Cytoskeleton Modifying Agents			
Approved Indication	Generic Name	Trade Name	Formulation
certain form of lung cancer*	paclitaxel albumin-bound particles	Abraxane	
Cell Signaling Inhibitors			
Approved Indication	Generic Name	Trade Name	Formulation
HER2+ breast cancer	ado-trastuzumab emtansine	Kadcyla	
certain type of lung cancer	afatinib	Gilotrif	
certain type of leukemia	bosutinib	Bosulif	
certain type of melanoma	dabrafenib	Tafinlar	
certain type of bone cancer*	denosumab	Xgeva	
certain types of leukemia	ponatinib	Iclusig	
certain types of melanoma	trametinib	Mekinist	
Immune System Modifiers			
Approved Indication	Generic Name	Trade Name	Formulation
certain type of lymphoma*	lenalidomide	Revlimid	
multiple myeloma	pomalidomide	Pomalyst	
Protein Translation Inhibitor			
Approved Indication	Generic Name	Trade Name	Formulation
certain type of leukemia	omacetaxine mepesuccinate	Synribo	
Radiation-emitting Drugs			
Approved Indication	Generic Name	Trade Name	Formulation
prostate cancer bone metastases	radium Ra 223 dichloride	Xofigo	

**New Technologies**

Imaging Agents			
Approved Indication/use	Generic Name	Trade Name	Formulation
imaging dense breasts	automated ultrasound	Somo-v-ABUS	
general imaging	"low-dose, high-resolution CT scanner"	Aquilion ONE Vision	
imaging lymphatics in breast cancer and melanoma	technetium Tc 99m tilmanocept	Lymphoseek	

\* New indication for 2013.

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



**Figure 2: I Will Survive.** The number of cancer survivors alive in the United States has steadily increased since 1971 [blue bars] (1-3). During the same period of time, the proportion of our nation's population that is living with, through, or beyond a cancer diagnosis has more than tripled [gold line] (1-3, 6).

It is projected that more than 1.6 million Americans will be diagnosed with cancer in 2013 (1). This number will dramatically increase in the next two decades, largely because cancer is primarily a disease of aging (1). Most cancer diagnoses occur in those aged 65 and older (1, 4), and this portion of the population is rapidly growing (6, 7) (see **Figure 3**, p. 7). Compounding the problem is the increasing prevalence of obesity and the continued use of tobacco products by nearly 20 percent of the U.S. population, both of which are linked to an elevated risk for several cancers (8, 9). Given these compelling statistics, cancer prevention represents an area of particular

**Change in Death Rates for ALL MALIGNANT CANCERS (1990-2009)**

**24.5%**

♂

**15.8%**

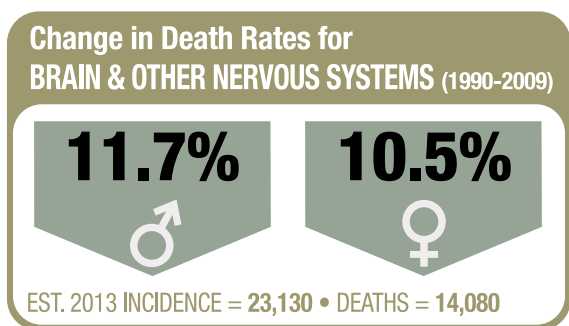
♀

EST. 2013 INCIDENCE = 1,660,290 • DEATHS = 580,350



promise because it is estimated that more than half of the cancer deaths that occur in the United States are preventable through lifestyle modifications (10).

Cancer is not unique to America; it is a global problem. Cancer incidence worldwide is predicted to increase from 12.8 million new cases in 2008 to 22.2 million in 2030 (11). Without the development of more effective preventive interventions and treatments, this will translate to more than 13 million lives claimed by cancer in 2030 (12).

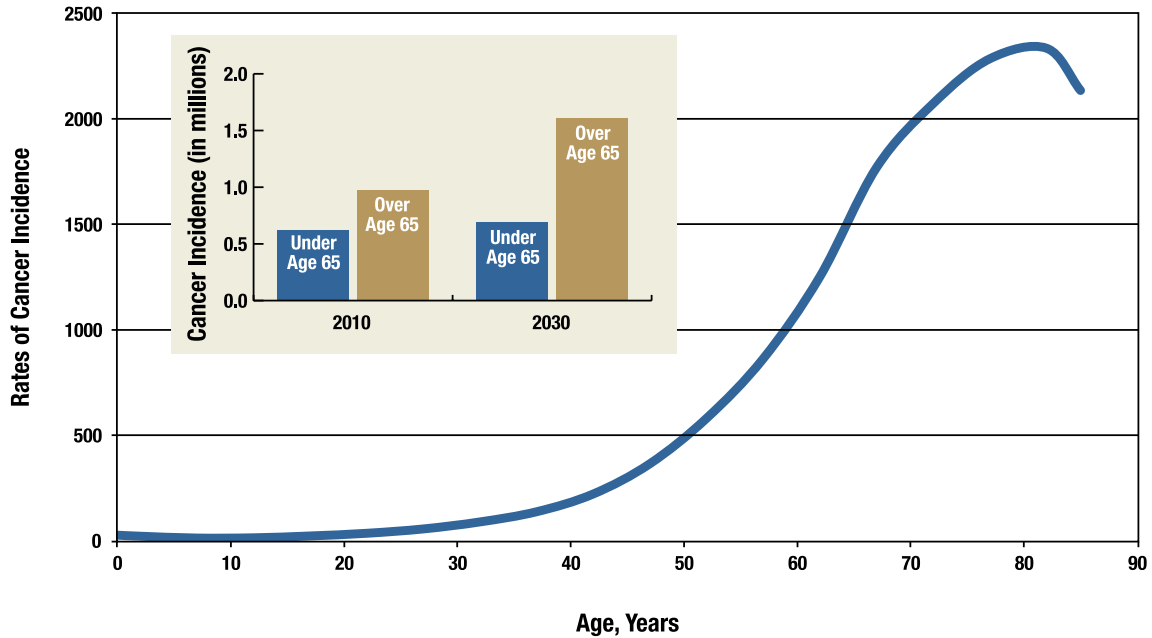


**Table 2: Select Cancer Incidence, Mortality, and Change in Death Rates (1990-2009)\***

Cancer type	Estimated 2013 incidence total <sup>^</sup>	Estimated 2013 deaths total <sup>^</sup>	Change in Death Rate (1990-2009)	Change in Death Rate (1990-2009)
			◀ DECREASING	0% INCREASING ▶
<b>All Malignant Cancers</b>	<b>1,660,290</b>	<b>580,350</b>	<b>-24.5</b>	<b>-15.8</b>
Head and Neck Region				
Brain & other nervous system	23,130	14,080	-11.7	-10.5
Oral cavity & pharyngeal	41,380	7,890	-35.1	-35.5
Laryngeal	12,260	3,630	-34.7	-22.2
Lung & bronchus	228,190	159,480	-32.0	+4.8
Breast	234,580	40,030	-32.9	
Gastrointestinal (GI) Tract				
Esophageal	17,990	15,210	-14.4	+4.3
Stomach	21,600	10,990	-46.8	-41.1
Liver & intrahepatic bile duct	30,640	21,670		+41.2
Pancreatic	45,220	38,460	-1.3	+3.0
Small intestine	8,810	1,170		
Colon and Rectal <sup>†</sup>	142,820	50,830	-38.1	-35.7
Urogenital System				
Kidney & renal pelvis	65,150	13,680		-6.7
Ovarian	22,240	14,030	-15.9	-9.4
Uterine (non-cervical)	49,560	8,190		-3.9
Cervical (uterine)	12,340	4,030	-37.4	
Urinary bladder	72,570	15,210		-10.7
Prostate	238,590	29,720	-42.6	-3.8
Testicular	7,920	370		
Melanoma (skin)	76,690	9,480		-9.6
Hematological System				
Leukemia	48,610	23,720		-11.0
Lymphoma				-15.0
Hodgkin lymphoma	9,290	1,180	-43.5	-36.0
Non-Hodgkin lymphoma	69,740	19,020		-18.6
Myeloma	22,350	10,710		-22.2
Bones & joints	3,010	1,440		-12.4
Soft tissue (including heart)	11,410	4,390		-16.6

\* Data are rounded to the nearest 10; estimated new cases exclude basal cell and squamous cell skin cancers and in situ carcinomas except urinary bladder. † Estimated incidence and 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), representing about 98% of the US population. Estimated deaths are based on US mortality data during 1995-2009, National Center for Health Statistics, Centers for Disease Control and Prevention.

<sup>^</sup> Combined male and female data



**Figure 3: Aging Baby Boomers Predicted to Drive up Cancer Incidence.** The majority of all cancer diagnoses are made in those aged 65 and older (blue line) (1, 4). In 2010, individuals in this age group made up 13 percent of the U.S. population (6). In 2030, when the baby boomers will be aged 65 or older, this segment will be nearly 20 percent of the population (6). This change will dramatically increase the total numbers of cancers diagnosed each year, with a 67 percent increase in cancer incidence anticipated for the segment of the population aged 65 or over (bars) (7).

## Cancer: An Expensive Disease. Biomedical Research: A Wise Investment

Of all major causes of disease worldwide, cancer has the greatest economic burden from premature death and disability. The global economic toll is 20 percent higher than that from any other major disease, at \$895 billion in 2008 (13). This figure does not include the direct costs of treating cancer. In the United States, the latest estimates from the NIH indicate that the overall economic costs of cancer in 2008 were \$201.5 billion: \$77.4 billion for direct medical costs and \$124.0 billion for lost productivity due to premature death (1).

Given that cancer is the most costly disease to our nation, and it is poised to become the number one killer of Americans, it is urgent that we increase our investments in the scientific research needed to develop more effective interventions. This report highlights many of the remarkable recent advances that are the direct result of the dedicated work of thousands of researchers funded through the federal government and other sectors of the biomedical research enterprise. There is little doubt that the ability of these researchers to continue making lifesaving progress is in significant jeopardy given that NIH and NCI budgets are decreasing (see **Funding Cancer Research and Biomedical Science Drives Progress**, p. 69).

# What is Cancer?

## In this section you will learn:

- Cancer is not one disease, but likely more than **200 different** types of the disease.
- **Changes in the genetic material** in a cell underpin cancer initiation and development in most cases.
- A cancer cell's **surroundings influence** the development and progression of disease.
- The development of **cancer is a process** that occurs over a period of many years.
- The most advanced stage of cancer, **metastatic disease**, accounts for more than **90 percent of cancer deaths**.

## Five Molecularly Targeted Therapies

imatinib, dasatinib, nilotinib, bosutinib, and ponatinib — block the abnormal protein that causes most cases of chronic myelogenous leukemia, BCR-ABL.

At its simplest, cancer can be considered a disease in which normal cells start “behaving badly”, multiplying uncontrollably, ignoring signals to stop, and accumulating to form a mass that is generally termed a tumor (see **Developing Cancer**, p. 17).

Unfortunately, research has taught us that cancer is anything but simple.

First and foremost, there are perhaps as many as 200 different types of cancer, each named for the organ or type of cell from which it originates. Moreover, cancer is complex at every level, from populations, to individuals, to specific cancers, to the molecular and genetic defects that drive these cancers.

Despite cancer’s complexity, we are beginning to exploit our growing knowledge of the molecular changes that generally drive cancer initiation and development for the benefit of patients, providing new ways to reduce the burden of cancer (see sidebar on **The Virtuous Cycle of Biomedical Research**, p. 9).

## The Origins of Cancer

An in-depth understanding of what happens when normal cells become cancerous is essential if we are to answer the question: What is cancer?

We know that to keep our bodies healthy, most cells multiply or divide in a tightly controlled process to replace old and damaged cells. Sometimes, this well-regulated process goes awry, and cells do not die when they should or new cells form when they should not. These extra cells can accumulate, forming a tumor. What upsets this delicately balanced system and causes cancer?

## The Virtuous Cycle of Biomedical Research

All biomedical research, including cancer research, is an iterative cycle, with observations flowing from the laboratory bench to the patient's bedside and back to the laboratory again. Essential to this cycle is the participation of not only basic scientists, physician-scientists, and clinical researchers, but also patients and their health care providers.

In short, the cycle is set in motion when observations are made and then questions are asked and tested. This can lead to discoveries that have the potential to be converted into a tangible tool, drug, or agent to be studied in the clinic. In addition, these discoveries can feed back through the research cycle. Testing of a discovery in the clinic can either lead to a new approach for the prevention, detection, diagnosis, or treatment of disease, or can generate a new observation to be run back through the research cycle.

Observations come from various sources. For example, basic scientists, physician-scientists, and clinical researchers study animals, cells, patients, patient samples, and/or molecules to learn how the body naturally functions and how these functions change during disease. Epidemiologists study groups of people looking for associations between patterns of risk factors or diseases and their relationship to health outcomes.

In each case, an observation helps generate a question, also known as a hypothesis. Researchers then try to answer this question through a series of tests or experiments. In preclinical testing, these experiments are carried out in the laboratory using experimental models of disease; while in clinical testing, the experiments are carried out primarily in patients and sometimes in animals that naturally develop human diseases.

Experimental models mimic what happens in healthy and disease conditions, and come in many forms ranging from isolated cells to whole animals. These cells can come directly from patients or may be more "permanent" cell lines that have been genetically engineered for the purpose at hand. Cells can be studied in isolation, together with other cell types, or combined with animal models for further testing. A number of animals are used in research including mice, zebrafish, flies, and worms.

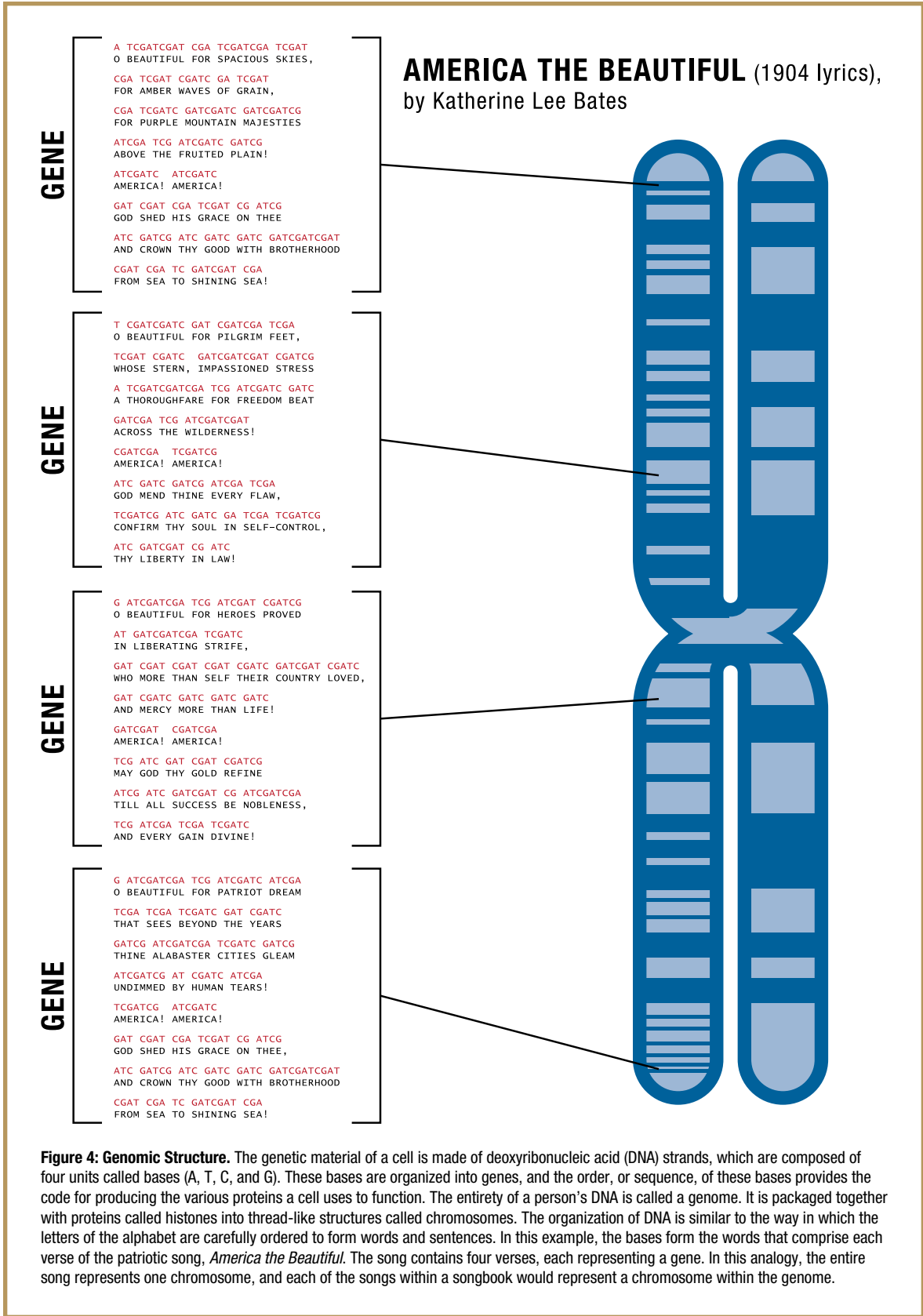
The study and manipulation of experimental models — for example, exposing them to a potential new drug — can help identify useful approaches for disease prevention, detection, diagnosis, or treatment that can then be tested in the clinic. Various techniques are used to probe cancer models, including but not limited to: genetic, biochemical, and cellular analyses.

Finally, before a tool, drug, or agent developed in the laboratory can be routinely used in patient care, it must be rigorously tested in clinical trials. To evaluate the safety and efficacy of a potential therapy, it is typically evaluated in a series of clinical trials, each with an increasing number of patients. Individuals participating in clinical trials are closely monitored using a variety of methods to determine if the therapy is effective against their disease, and to watch for any potential adverse outcomes.

If a therapy is deemed to be safe and effective, then it will be approved by the appropriate regulatory agencies for broader commercial use. It is also important to note, however, that all observations, positive or negative, are essential to the research cycle. For example, in cases where there is no immediate clinical benefit observed in a clinical trial, the knowledge amassed during the trial can be probed for insights into why and how a therapy may have failed to provide the expected effect. This can provide key insights into how the approach may be improved.

Because research is an iterative cycle, regulatory approval is not the end of the line. It is vital that what happens at patients' bedsides feeds back into the research cycle. For example, even if clinical trials indicate that an agent, drug, or tool can help reduce the burden of cancer and it is adopted into routine clinical practice, continued monitoring of its safety and benefits provides important information for improved use and further innovation.

If the iterative cycle of research is to be truly successful, no segment of the research cycle or single research discipline can operate in isolation. Insights from all disciplines influence others, and discoveries in one disease area can offer new ideas for the conquest of other diseases (see Sidebar on **Cancer Research at Work Against Other Diseases**, p. 46).



**Figure 4: Genomic Structure.** The genetic material of a cell is made of deoxyribonucleic acid (DNA) strands, which are composed of four units called bases (A, T, C, and G). These bases are organized into genes, and the order, or sequence, of these bases provides the code for producing the various proteins a cell uses to function. The entirety of a person's DNA is called a genome. It is packaged together with proteins called histones into thread-like structures called chromosomes. The organization of DNA is similar to the way in which the letters of the alphabet are carefully ordered to form words and sentences. In this example, the bases form the words that comprise each verse of the patriotic song, *America the Beautiful*. The song contains four verses, each representing a gene. In this analogy, the entire song represents one chromosome, and each of the songs within a songbook would represent a chromosome within the genome.

## The Genetic Basis of Cancer

Changes, or mutations, in the genetic material of normal cells can disrupt the balance of factors governing cell survival and division, and lead to cancer. This discovery, which was primarily enabled through NIH funding, was one of the greatest research advances in the modern era.

The genetic material of a cell is made of deoxyribonucleic acid (DNA) strands, which are composed of four units called bases. These bases are organized into genes, and the order, or sequence, of these bases provides the code for producing the various proteins a cell uses to function. The organization of DNA is similar to the way in which letters of the alphabet are carefully ordered to form words and sentences (see **Figure 4**, p. 10).

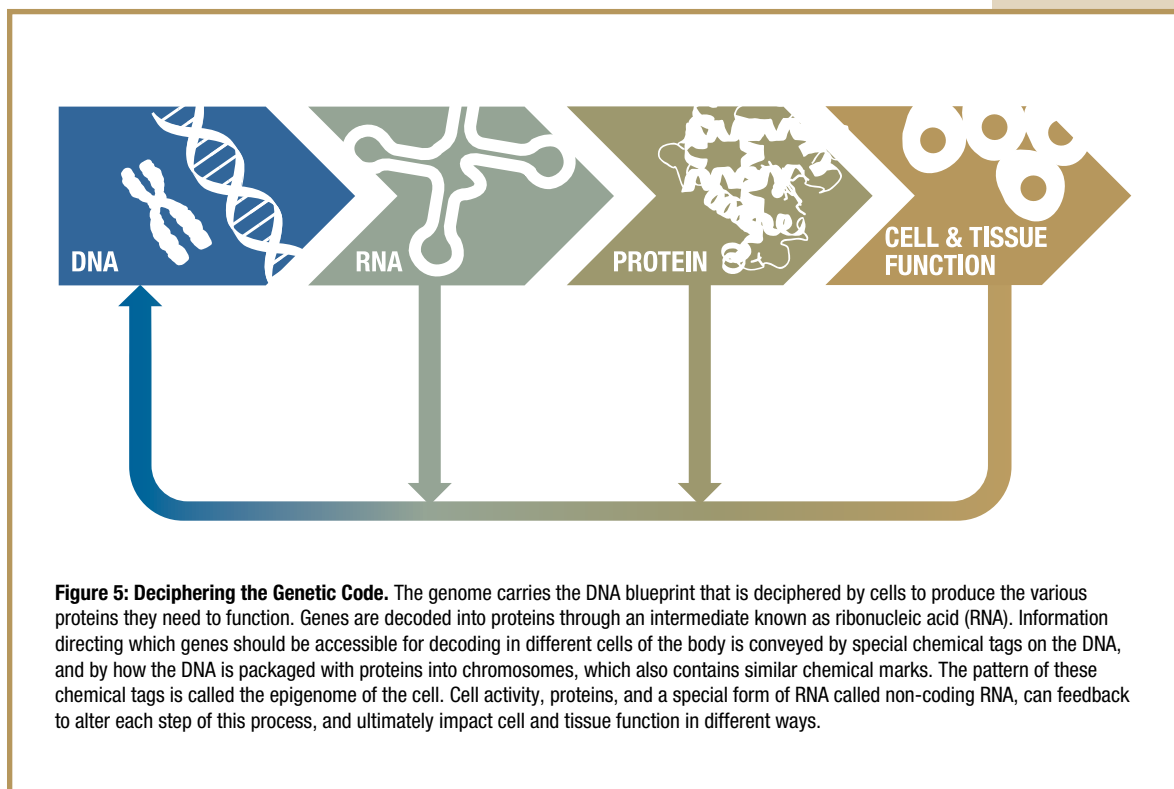
The entirety of a person's DNA is called a genome. Almost every cell in the body contains a copy of the genome, which is packaged together with proteins called histones into thread-like structures called chromosomes. In the analogy of the written word, the genome and chromosomes are similar to a story and the chapters that make up that story, respectively (see **Figure 4**, p. 10).

Since a cell deciphers the DNA code to produce the proteins it needs to function, mutations in the code can result in altered protein amounts or functions, ultimately leading to cancer (see **Figure 5**).

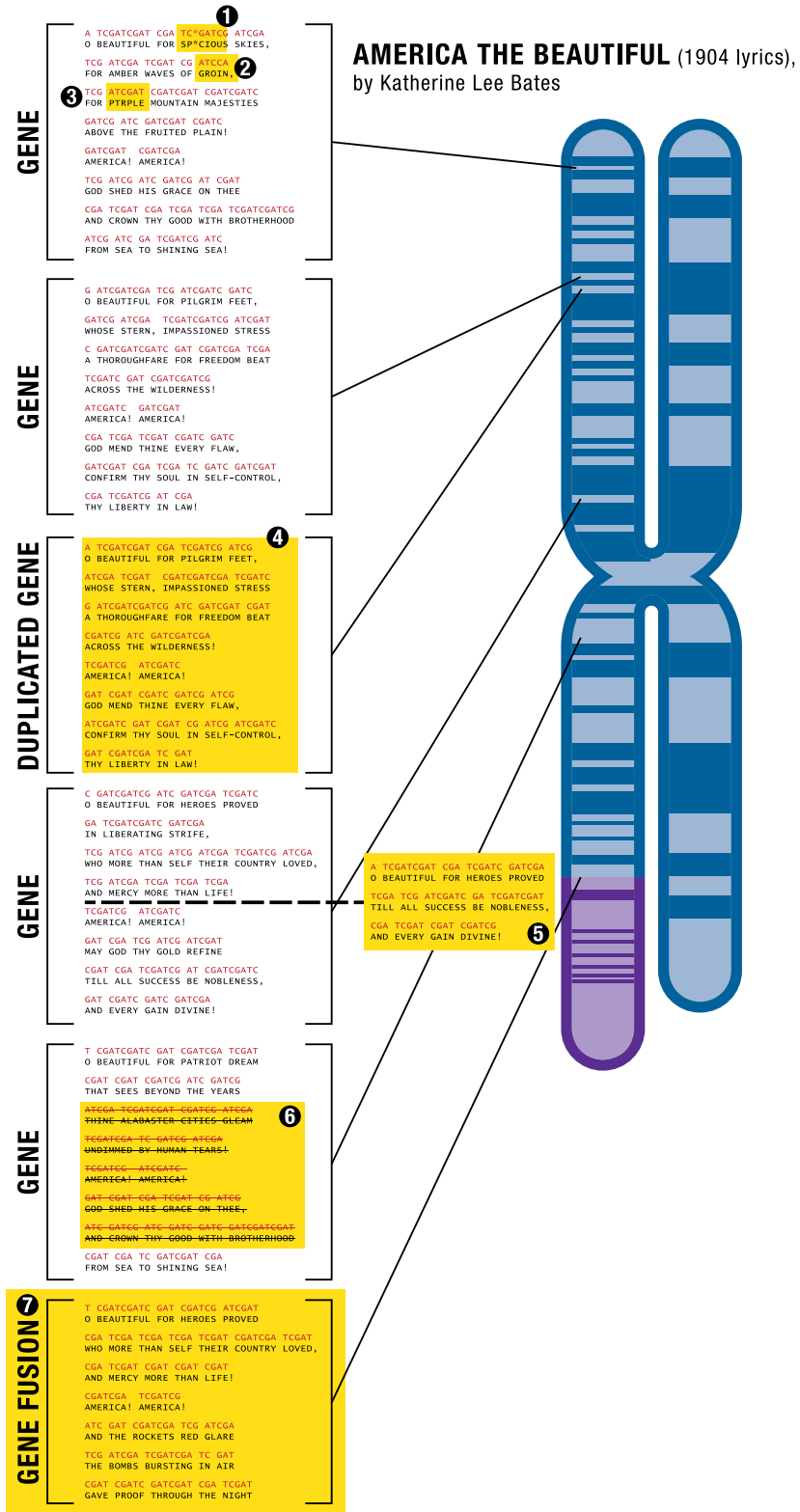
There are many different types of mutations that can cause cancer. These range in size from a single base change (a letter is out of order or missing) to extra copies of a gene (a paragraph is repeated many times) to the deletion of a large segment of a chromosome (part of a chapter is missing) (see **Figure 6**, p. 12). Further, chromosomes can break and recombine, resulting in the production of entirely new proteins, like the one that causes most cases of chronic myelogenous leukemia (CML) and the one that leads to about 5 percent of non-small cell lung carcinomas.

## Crizotinib

The molecularly targeted therapy **crizotinib** blocks the abnormal protein that leads to about 5 percent of non-small cell lung carcinomas, EML4-ALK.



**Figure 6: The Impact of Genetic Mutations.** Since a cell deciphers the DNA code to produce the proteins it needs to function (see **Figure 5**, p. 11), mutations in the code can result in altered protein amounts or functions, ultimately leading to cancer. It should be noted that not all mutations are harmful nor do they always lead to cancer. There are many different types of mutations that can cause cancer. Using the analogy of the written word (see **Figure 4**, p. 10), in the first line of *America The Beautiful*, a single letter (base) deletion has made the word spacious unreadable [1]; such a change would also affect how the remainder of the bases in the gene are read (not illustrated). Large deletions can also occur and alter the meaning of the verse (gene), like the deletion in the fourth verse [6]. In the second line of the song, a substitution mutation has changed the word grain to groin, thus changing the meaning of the line [2]. Not all substitution mutations change the meaning, as in the example in the third line [3]. Other mutations can lead to duplications, also known as amplifications, of an entire gene; here, the second verse has been amplified [4]. Chromosomes can also break and recombine, resulting in new genes and the production of entirely new proteins. The last verse has been broken and recombined with a piece from a different song, leading to a completely new verse [7]. Changes in the epigenome can make regions of the genome accessible for use when they shouldn't be, or inaccessible when they should be available. If the page were folded on the dotted line, the third verse would lose five lines [5].



Over the years, researchers have determined that cancer-associated genetic mutations are most often found in one of two classes of genes: proto-oncogenes and tumor suppressor genes. These genes normally regulate the natural processes of cell growth and death to keep our tissues and organs healthy.

Mutations in proto-oncogenes change them into oncogenes that result in altered proteins that can drive the initiation and progression of cancer. These altered proteins usually work by over activating the normal networks that drive cell division and survival; some can be directly targeted by precision medicines.

Tumor suppressor genes code for proteins that normally stop the emergence of cancer by repairing damaged DNA or by restraining signals that promote cell survival and division. Mutations in these genes typically inactivate them and can result in the production of dysfunctional proteins that do not stop the accumulation of harmful mutations or that allow overactive cells to survive, causing cancer to develop.

The understanding that cancer can be caused by genetic changes that lead to altered proteins and disruption of normal cell behaviors has spurred the development of cancer drugs that target these proteins. This approach, treating cancer patients based on the genetic and molecular profile of their cancer, is referred to as personalized cancer medicine, molecularly based medicine, precision medicine, or tailored therapy. Although it is a relatively new concept, it is already transforming the prevention, detection, diagnosis, and treatment of cancer.

### **Beyond Genetics: The Role of Epigenetics**

It is clear that mutations in the genome of a normal cell can lead to cancer. However, recent research has shown that changes in the regions of the genome available for use by a cell also influence the development of cancer. To return to the analogy of a book, these changes in genome accessibility alter how the book is read; for example, creating a page to hide one

or more sentences. Understanding how these changes arise and how they affect cellular functions is part of the field of research called epigenetics.

Each cell in an individual contains the same 25,000 genes. Natural differences in genome accessibility, which generate different patterns of gene usage, lead to the diverse array of cell types in our bodies. Special chemical marks on DNA and histones together determine genome accessibility, and thus gene usage, in a given cell type. The sum of these chemical marks, called epigenetic marks, is referred to as the epigenome.

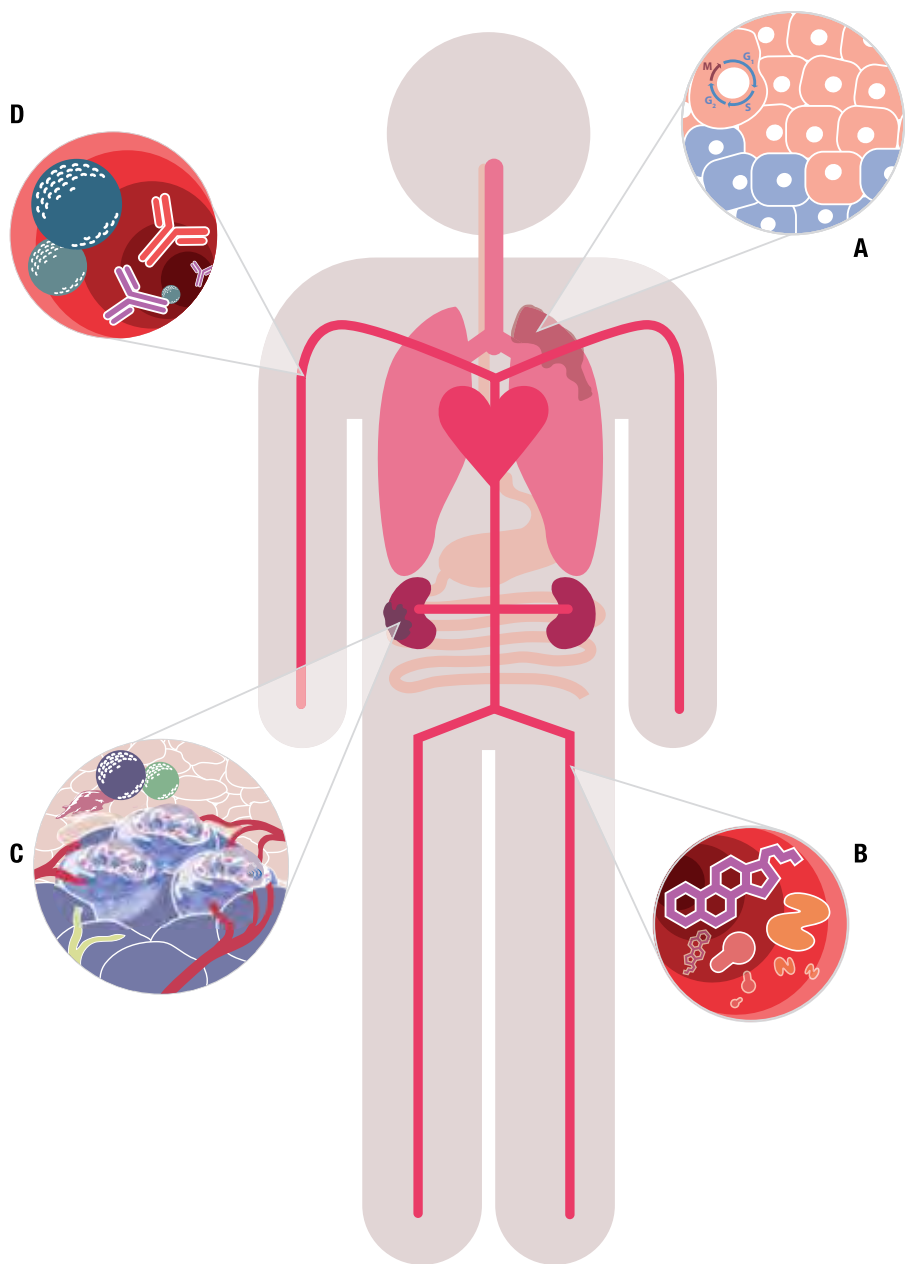
Most cancer cells have profound abnormalities in their epigenomes when compared with normal cells of the same tissue. In many cases, these epigenetic defects work in conjunction with permanent changes in the genetic material of the cell to promote cancerous behaviors.

One of the most exciting discoveries is that some epigenetic abnormalities are reversible. As a result, researchers are exploring whether therapies that work by reversing specific epigenetic defects can be used to treat cancer. The potential of this concept is highlighted by the fact that there are already four FDA-approved epigenetic drugs, which are used to successfully treat some patients with lymphoma or preleukemia who are nonresponsive to traditional chemotherapy. With efforts underway to map the epigenetic changes in all major types of cancer, it seems likely that more epigenetic drugs are destined to benefit many more patients in the near future and for years to come.

## **Epigenetic Therapies**

Patterns of DNA methylation and histone acetylation, which are epigenetic marks that control genome accessibility, are modified in many cancer cells. The FDA has approved the DNA methylation inhibitors azacitidine (Vidaza) and decitabine (Dacogen) for the treatment of myelodysplastic syndrome. Likewise, the histone deacetylase inhibitors romidepsin (Istodax) and vorinostat (Zolinza) are FDA-approved for the treatment of certain lymphomas.





**Figure 7: Cancer Growth: Local and Global Influences.** The initiation and growth of a cancer occurs locally and is largely due to accumulation of genetic changes that lead to defects in the molecular machinery of cells, permitting them to multiply uncontrollably and survive when normal cells would die (see **The Origins of Cancer**, p. 8). Uncontrolled proliferation occurs when normal control of a tightly regulated cellular process called the cell cycle is lost (A). Cancer is not only a local disease, but also a disease of the whole body, as interactions between cancer cells and their environment strongly influence cancer development and growth. For example, systemic factors in the circulation such as hormones and nutrients affect these processes (B), as does the cancer's ability to stimulate the creation of new blood vessels and lymphatic vessels, which bring in nutrients as well as provide a route for cancer cell escape to distant sites (metastasize) (C), and its capacity to manipulate the immune system (D). Importantly, none of these factors works in isolation, but altogether as a large network.

## Outside Influences

It is clear that cancer develops as a result of alterations to the genetic material of a cell that cause malfunctions in its behavior. Research has revealed, however, that cancer cannot be understood simply by characterizing the abnormalities within cancer cells. Interactions between cancer cells and their environment, known as the tumor microenvironment, as well as interactions with the person as a whole, profoundly affect and can actively promote cancer development (see **Figure 7**, p. 14). This means that cancer is much more complex than an isolated mass of proliferating cancer cells, which adds immense complexity to the answer to the question: What is cancer?

Key components of the tumor microenvironment include the matrix of proteins that surrounds the cancer cells, blood and lymphatic vessels, nutrients, hormones, and the immune system. Some of these cancer-influencing factors are normal parts of the tissue in which the cancer is growing, for example, the protein matrix surrounding the cancer cells. Others, such as hormones and nutrients, percolate and act throughout the body, including the tumor microenvironment. Yet others are actively recruited or formed as a result of signals emanating from the cancer cells; for example, many cancer cells release molecules that trigger the growth of new blood and lymphatic vessels. Whether passive participants or active recruits, the various components of the microenvironment are often used by cancers to advance their growth and survival.

The immune system and the blood and lymphatic vasculature are not only important elements of the tumor microenvironment that shape the course of cancer, but are also global factors that affect the whole body. Therefore, if we are to advance our mission to prevent and cure all cancers, we must develop a more comprehensive, whole-patient picture of cancer.

## The Immune System

The immune system can be considered an integrated network of organs, tissues, cells, and cell products that protects our bodies from disease-causing pathogens. For example, it is responsible for clearing the viruses that cause the common cold and the bacteria that lead to some forms of meningitis.

Only about 2 percent of immune cells are circulating in the blood at any given time; the rest are percolating through our tissues, including any tumors that are present, constantly on patrol. As it does with pathogens, the immune system can identify and eliminate cancer cells. Clearly, this function of the immune system sometimes fails, and some cancer cells evade the immune system, forming tumors. As researchers have learned more about the components of the immune system and how they interact with cancer cells, they have been able to design therapies that modify a patient's immune system to make it capable of destroying the patient's cancer cells. Progress in this critical area of cancer treatment is highlighted in this report in the **Special Feature on Immunotherapy** (see p. 38).

While some immune responses have anticancer effects that can be exploited for cancer treatment, research has established that other immune responses can, instead, promote cancer development and progression in some situations (14). For example, persistent inflammation, which occurs as a result of constant stimulation of the immune system, creates an environment that enables cancer formation, growth, and survival. Infection with pathogens such as hepatitis B or C viruses, as well as continual exposure to toxins like alcohol or asbestos, can cause this destructive persistent inflammation.

Since the immune system has both tumor-promoting and antitumor functions, we need to learn more about its intricacies if we are to fully exploit it for patient benefit. This will only be achieved through more research into this promising area of science.

## Hepatitis C Virus Screening

In June 2013, the United States Preventive Services Task Force (USPSTF) recommended one-time hepatitis C virus (HCV) screening for those born from 1945 to 1965, as well as for individuals at high risk of infection, such as injection drug users and those who received blood transfusions before 1992.

## 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. Examples include chronic myelogenous leukemia, non-Hodgkin lymphoma, and multiple myeloma.

## Solid Cancers

Cancers that arise in tissues other than the blood can be grouped depending on the type of cell they originate from in that tissue. Examples include:

- carcinomas, which begin in the skin or in tissues that line or cover internal organs;
- sarcomas, which arise from cells of the bone, cartilage, fat, muscle, blood vessels, or other connective or supportive tissue; and
- blastomas, which derive from immature “precursor” cells or embryonic tissue.

### Blood and Lymphatic Vessel Networks

Like normal cells, cancer cells require nutrients and oxygen to rapidly grow and survive. They must also get rid of the toxic substances they generate through their use of these fuels. To achieve these goals, many cancer cells promote the growth of new blood and lymphatic vessels, processes called angiogenesis and lymphangiogenesis, respectively.

Among the many molecules cancer cells use to induce angiogenesis and lymphangiogenesis is a family of growth factors called VEGFs. These molecules attach to proteins on the surface of the cells that form blood and lymphatic vessel walls, stimulating vessel growth.

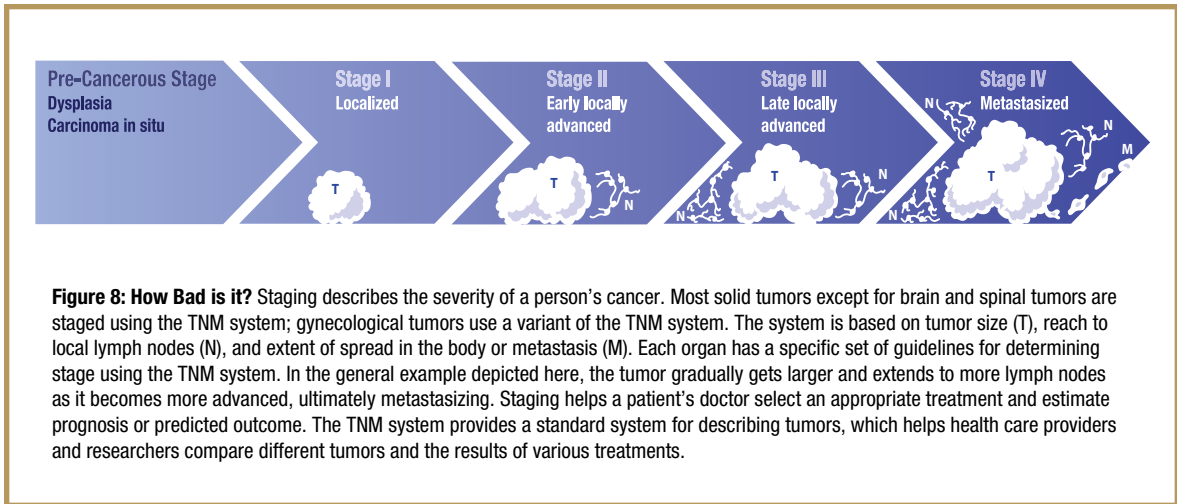
Some cancers are more dependent than others on the growth of new blood and lymphatic vessels to thrive. These cancers, such as the most common type of kidney cancer in adults (renal cell carcinoma), are particularly susceptible to a group of drugs that target the VEGFs or the proteins to which VEGFs bind, the VEGF receptors, impeding blood and lymphatic vessel growth (see **Table 3**).

In addition to nourishing tumors, the new network of blood and lymphatic vessels provides a route by which cancer cells can escape their primary location. Once cancer cells enter the vessels, they have the potential to move to and grow in other areas of the body where they can establish new tumors; this is called metastasis. Metastasis is responsible for more than 90 percent of the morbidity and mortality associated with cancer.

**Table 3: Currently Approved Angiogenesis Inhibitors for the Treatment of Cancer**

Approved Indication	Generic Name	Trade Name	Formulation
Kidney cancer	axitinib	Inlyta	
Colon; kidney; and lung cancers	bevacizumab	Avastin	
Kidney cancer; soft tissue sarcomas; gastrointestinal stromal tumors	pazopanib	Votrient	
Colorectal cancer; gastrointestinal stromal tumors	regorafenib	Stivarga	
Kidney cancer	sorafenib	Nexavar	
Gastrointestinal stromal tumors; kidney cancer; some pancreatic cancers	sunitinib	Sutent	
Thyroid cancer	vandetanib	Caprelsa	
Colorectal cancer	ziv-aflibercept**	Zaltrap	

\*\*modified antibody



## Developing Cancer

Many cancers, particularly those that arise in tissues other than the blood, are progressive in nature (see **Figure 8**). They begin with one or more changes to the genetic material of normal cells. These mutations continue to accumulate over time, first turning normal cells into precancerous cells, which multiply to form precancerous lesions. As more mutations arise within a precancerous lesion, some cells evolve into cancer cells, further dividing to form a tumor. Further mutations can cause some cancer cells to become capable of metastasizing, leading to the emergence of metastatic cancer.

Metastatic disease is a dire occurrence that almost inevitably leads to death. A fundamental understanding of this process is essential to conquering cancer. Research over the past few decades has just begun to teach us why metastatic disease is so difficult to treat. To begin, metastasis is a complex, multistep process, and virtually every step can be achieved through multiple different pathways. Thus, obstructing only one pathway therapeutically is generally insufficient to stop the entire process. Compounding this problem is the fact that cancer cells can travel to other parts of the body before the initial tumor is found, and then lie dormant in this location, becoming active years later to form a metastatic tumor. Currently, we do not know enough about cancer cell dormancy to either efficiently locate and eliminate these cells or design therapies that could prevent them from reawakening, facts that underscore the critical need for further research in these areas.

Improvements in our understanding of the development of cancer have allowed us to detect some precancerous lesions and intercept them before they become life-threatening. For example, in the cervix, precancerous lesions are called cervical intraepithelial neoplasia. These can be detected using the

Papanicolaou (Pap) test and can be removed or destroyed by several procedures including cryocautery, electrocautery, and laser cautery.

It is clearly advantageous to detect and stop cancer as early as possible in the course of its development, particularly prior to metastasis. Currently, we successfully do this for some cancers. Only through more research will we be able to apply this approach more generally to cancers that kill. We obviously must support the research needed to fully understand the metastatic process if we are to ultimately cure and control all cancers.

# Prevention and Early Detection

## It's Never Too Late to Quit

using tobacco. Quitting even after a cancer diagnosis can reduce complications associated with cancer treatment and improve overall survival. The AACR recommends that healthcare providers assess tobacco use by cancer patients in all clinical settings and provide users with cessation treatment. The AACR also encourages researchers to study how tobacco use by clinical trial participants changes treatment outcomes in trials. Read more at: [www.aacr.org/tobacco](http://www.aacr.org/tobacco).

### In this section you will learn:

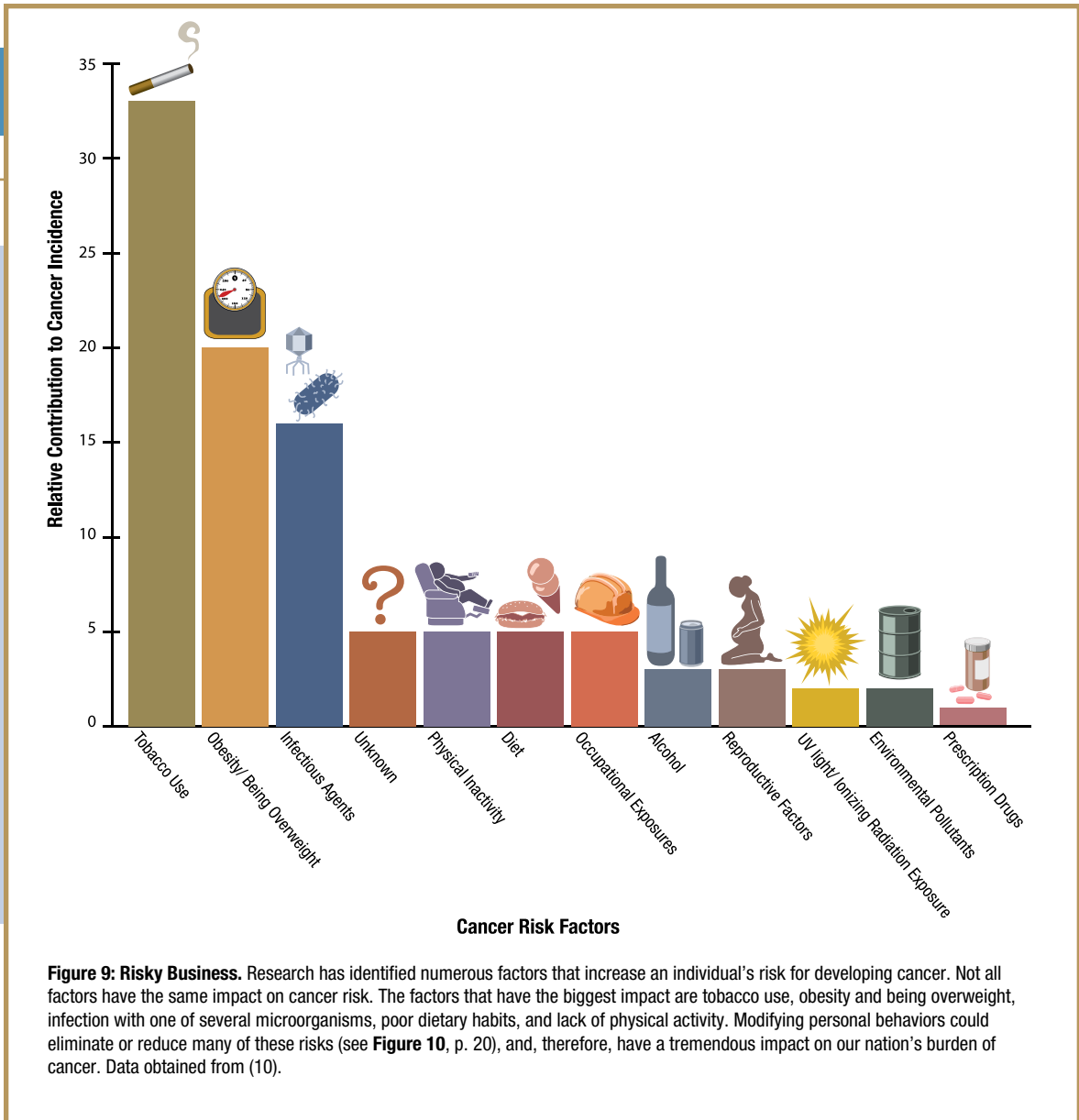
- More than **half of cancer deaths** in the United States are a result of preventable causes.
- **Obesity and type 2 diabetes mellitus significantly increase** the incidence and worsen outcomes of some forms of cancer.
- Sufficient levels of **physical activity** reduce the incidence of certain cancers and improve their outcomes.
- Tobacco use is responsible for almost **30 percent of cancer deaths** in the United States.
- **Disparities in colorectal cancer incidence and mortality can be reduced** by making colonoscopy available to all who are eligible.
- Identifying individuals at **highest risk** for developing certain cancers can make screening more effective.

Many of the greatest reductions in the morbidity and mortality of cancer have come from advances in cancer prevention and early detection. These remarkable effects were achieved by translating advances in our understanding of the causes and progressive nature of cancer into effective new clinical practices, and public education and policy initiatives.

Changes in the clinic include improved screening practices (e.g., colonoscopy to detect and remove precancerous adenomatous polyps) and the introduction of targeted interventions (e.g., administering vaccines to prevent infection with pathogens associated with cancer risk, such as hepatitis B virus or human papilloma viruses). Likewise, public education regarding common factors that increase cancer risk (such as physical inactivity and unhealthy diets) have also played a role, as has the implementation of policies aimed at promoting healthier lifestyles and minimizing exposure to cancer-causing agents (such as tobacco smoke and asbestos).

### Healthy Living Can Prevent Cancer

Decades of research have led to the identification of numerous factors that affect a person's risk of developing cancer (see **Figure 9**, p. 19). Through this work, scientists have come to the conclusion that more than 50 percent of the 580,350 cancer deaths expected to occur in the United States in 2013 will



be related to preventable causes such as tobacco use, obesity, poor diet, and lack of physical activity (10). Modifying personal behaviors (see **Figure 10**, p. 20) to eliminate or reduce these risks, where possible, could, have a tremendous impact on our nation’s burden of cancer. However, a great deal more research and resources are needed to understand how to best help individuals to change their lifestyle.

**Eliminating High-Risk Activities**

Everyone could dramatically reduce their risk of certain cancers by making two changes to the ways they live: cutting out tobacco products and avoiding excessive exposure to

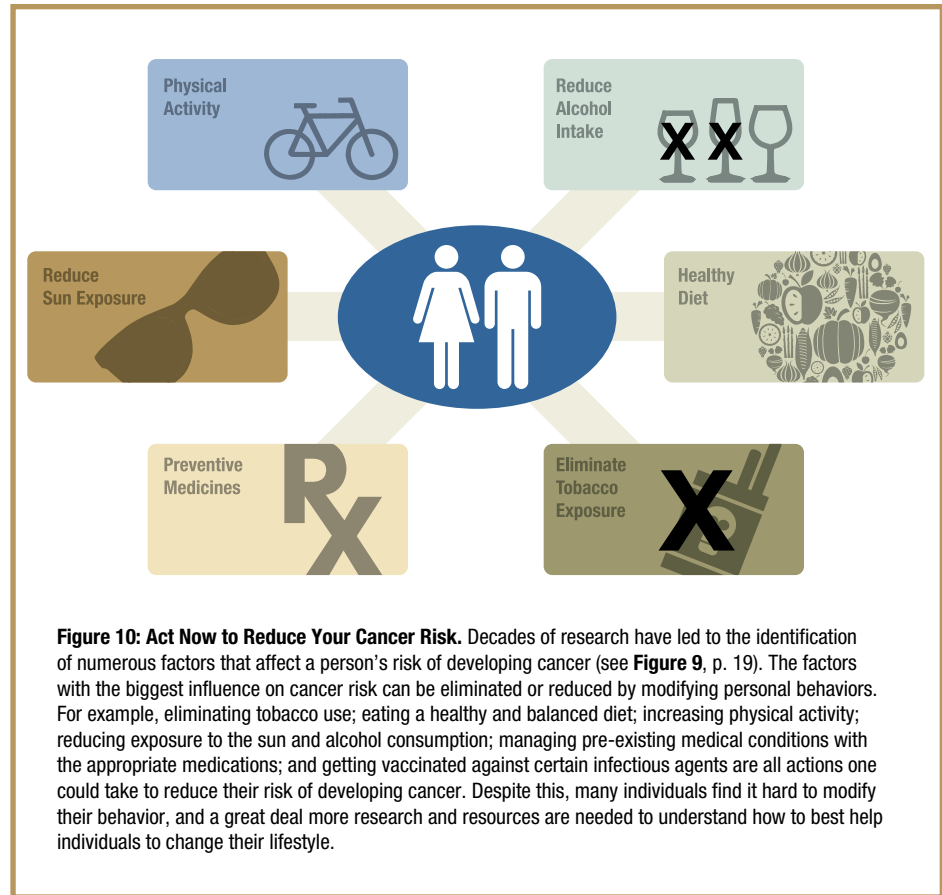
ultraviolet (UV) light, a form of damaging radiation emitted by the sun, sunlamps, and tanning beds. Making these changes not only reduces the chances of developing certain cancers, but can also reduce cancer recurrence or improve outcomes following a cancer diagnosis.

**Tobacco Use and Cancer**

The scientifically established causal relationship between cigarette smoking and lung cancer was first brought to the public’s attention in 1964, when the “U.S. Surgeon General’s Report on Smoking and Health” was published (15). This report set in motion major policy changes, media campaigns, and

## More Than 20X

Tobacco smoke is a well-established carcinogen, with smokers **more than 20-times** more likely to develop lung cancer than nonsmokers (18). Research will help us better understand why some individuals develop cancer with relatively little exposure to smoke, while others are more resistant to cancer development.



other measures to combat cigarette smoking in the United States (see **Table 4**, p. 21). As a result of these efforts, the prevalence of smoking decreased from 42 percent of Americans in 1965 to 18 percent in 2012 (16). This decrease has been credited with saving millions of lives that would otherwise have been lost not only to lung cancer, but also to 17 other types of cancer directly related to tobacco use (9) (see **Figure 11**, p. 22).

Even armed with this information, 70 million Americans, including some who have been diagnosed with and/or are actively being treated for cancer, regularly use tobacco products. Further, every day in 2010, 6,500 Americans aged 12 years and older smoked their first cigarette and approximately 40 percent of this group, or 2,600 individuals per day, became regular smokers (17). This is why tobacco use will be responsible for an estimated 30 percent of all cancer deaths that occur in the United States in 2013 (1).

### Change in Death Rates for ORAL CAVITY & PHARYNGEAL CANCERS (1990-2009)

**35.1%**



**35.5%**



EST. 2013 INCIDENCE = 41,380 • DEATHS = 7,890

### Change in Death Rates for LARYNGEAL CANCER (1990-2009)

**34.7%**



**22.2%**



EST. 2013 INCIDENCE = 12,260 • DEATHS = 3,630

**Table 4: Anti-Tobacco Public Policies**

Year	Policy	Importance	Function
1964	First Surgeon General's Report	First public declaration of the link between smoking and disease	<b>EDUCATION</b>
1965	Cigarette Labeling and Advertising Act	Requires all cigarette packs to carry health warning labels	<b>WARNING</b>
1967	FCC Fairness Doctrine Messages on TV and Radio	Requires broadcast TV and radio stations to offer time for public service announcements to counter cigarette advertising	<b>EDUCATION</b>
1971	Ban on cigarette advertising on TV	Eliminates a source of significant advertising promoting cigarette use	<b>PROTECTION</b>
1971	Warning labels strengthened	Warning labels are strengthened due to mounting evidence of the adverse health effects of smoking	<b>WARNING</b>
1975	The Minnesota Clean Indoor Air Act	First statewide law requiring separate smoking and non-smoking areas for indoor public spaces	<b>PROTECTION</b>
1983	Bipartisan Federal Cigarette Tax Increase to \$0.16/pack	Price increases discourage smoking, particularly among the youth	↑\$
1986	Surgeon General's Report on Involuntary Exposure to Cigarette Smoke	Alerts the public that secondhand smoke is also harmful to health	<b>EDUCATION</b>
1988	Smoking banned on U.S. flights under two hours	Eliminates exposure of non-smokers to secondhand smoke	<b>PROTECTION</b>
1990	Smoking banned on all U.S. flights	Eliminates exposure of non-smokers to secondhand smoke	<b>PROTECTION</b>
1991-1993	Bipartisan Federal Cigarette Tax Increase to \$0.24/pack	Price increases discourage smoking, particularly among the youth	↑\$
1998	Master Settlement Agreement	Prohibits targeted marketing to youth and funds counter advertising campaigns	<b>PROTECTION</b>
2000	Smoking banned on all international flights leaving US	Eliminates exposure of non-smokers to secondhand smoke	<b>PROTECTION</b>
2000-2002	Bipartisan Federal Cigarette Tax Increase to \$0.39/pack	Price increases discourage smoking, particularly among the youth	↑\$
2009	Family Smoking Prevention and Tobacco Control Act	Bans the use of fruit flavoring in cigarettes, and give-aways like t-shirts and hats	<b>PROTECTION</b>
2009	Family Smoking Prevention and Tobacco Control Act	Gave the FDA authority to regulate tobacco products for the first time in the country's history	<b>PROTECTION</b>
2009	Bipartisan Federal Cigarette Tax Increase to \$1.01/pack	Price increases discourage smoking, particularly among the youth	↑\$
2010	The Affordable Care Act	Sets aside funds for smoking prevention efforts and strengthens access to cessation treatment	<b>PROTECTION</b>

While the link between smoking and disease is widely understood today, this was not always the case. Over the past 50 years, numerous policies have been enacted to educate the public on the issue and protect non-smokers from exposure to second-hand smoke. Further, these policies also aim to reduce smoking prevalence, particularly by discouraging youth initiation. Together, anti-smoking public policies have contributed to widespread understanding of the risks associated with tobacco use, but evidence points to the need for continued education and outreach efforts.

## Smokeless Tobacco

Tobacco comes in many forms. While smoking rates in the United States have declined, the use of **smokeless tobacco** has increased. Individuals are increasingly consuming both forms of tobacco, smokeless tobacco in settings where smoking is prohibited and cigarettes elsewhere. This “dual use” may actually increase tobacco exposure while reducing the effect of smoking bans and the likelihood of tobacco cessation.

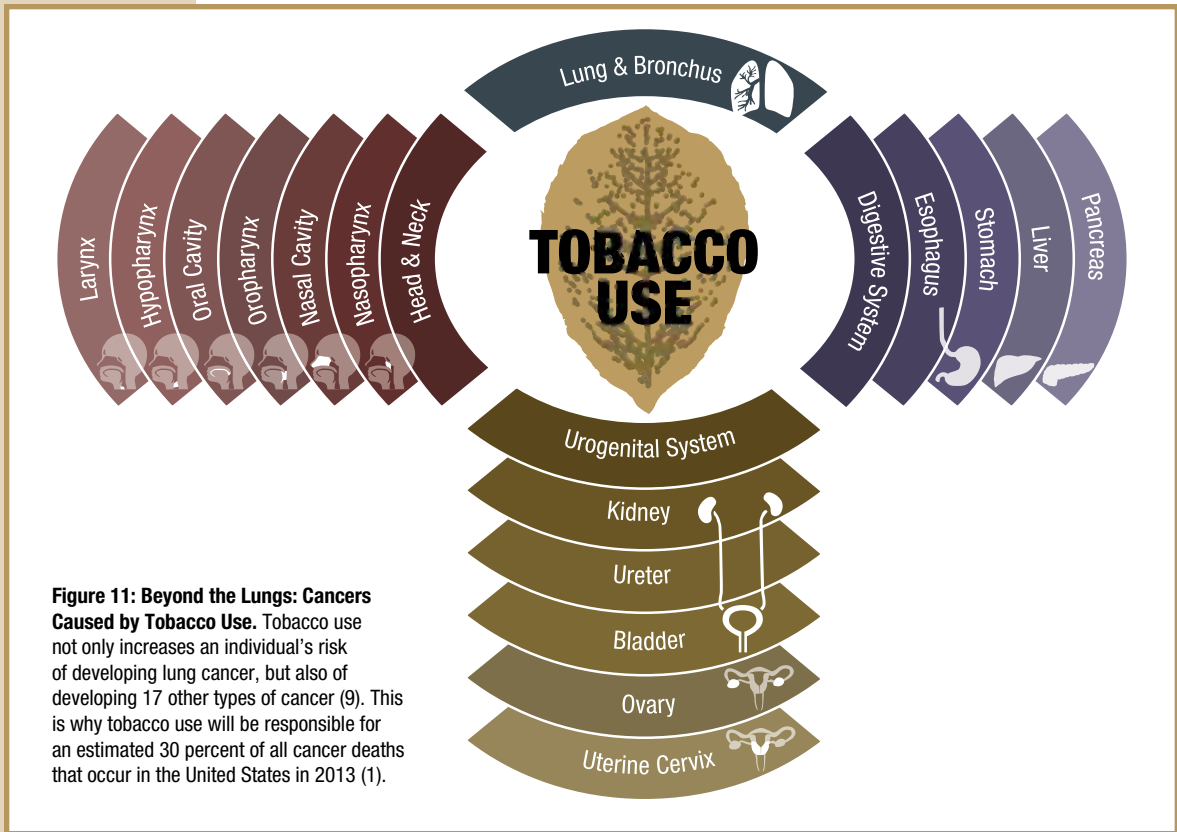
## 10 Years

You are 50 percent less likely to die of lung cancer **10 years** after stopping smoking.

## Five Years

You are 50 percent less likely to develop mouth, throat, esophageal, and bladder cancer **five years** after stopping smoking.





## Melanoma

accounts for the majority of skin cancer deaths in the United States but less than 5 percent of skin cancer cases (1).

## Exposure

Experts recommend that people seek shade and limit time in the sun, especially around midday; cover up with a shirt; wear a wide-brimmed hat; use sunglasses for eye protection; and apply a sunscreen rated SPF15 or higher at least every two hours.

It is not only the lives of those who use tobacco products that are at risk; scientific evidence has shown that exposure to secondhand tobacco smoke also causes cancer. This prompted the surgeon general to declare that there is no safe level of exposure to tobacco smoke (19). Although this has led to some important public health policies restricting smoking in public places (see **Table 4**, p. 21), smoking remains a huge threat to the public's health (20, 21). Countless lives could be saved through continued development and implementation of effective tobacco prevention, cessation, and control strategies.

### *Outdoor and Indoor Tanning and Cancer*

Exposure to UV light is the predominant cause of all three of the main types of skin cancer — basal cell carcinoma, squamous cell carcinoma, and melanoma. In fact, the International Agency for Research on Cancer (IARC), an affiliate of the World Health Organization, includes UV tanning devices and UV radiation from the sun in its highest cancer-risk category, “carcinogenic to humans” (22), alongside agents such as plutonium and cigarettes. Adopting sun-safe habits and avoiding the use of indoor UV tanning devices would dramatically decrease the incidence of skin cancer; for example, daily sunscreen use can cut the incidence of melanoma in half (23).

Despite the overwhelming scientific evidence that tanning bed use increases an individual's risk for developing cancer, particularly at a younger age (24, 25), tens of millions of Americans visit tanning salons each year (25). According to a 2011 report from the Centers for Disease Control and Prevention (CDC), this number includes more than 13 percent of all high school students and 21 percent of high school girls (27, 28). Responding to the clear cancer risk posed by tanning beds, the FDA has proposed reclassifying tanning beds into a more stringent category of medical products that would require warning labels to advertise their role in increasing skin cancer risk.

Preventing skin cancer by protecting skin from UV light exposure would not only limit the morbidity and mortality caused by these conditions, but would also save enormous amounts of money. It has been estimated that the total direct cost associated with the treatment of melanoma in 2010 was \$2.36 billion in the United States (28). Given that melanoma incidence rates continue to increase (1), patients, researchers, and politicians seeking to balance their budgets need to come together to develop and implement more effective policy changes and public education campaigns to help reduce the health and economic burdens of skin cancer.

### Cancer-associated Infectious Agents

Persistent infection with one of several pathogens is an important cause of about 20 percent of cancers worldwide (29, 30) (see **Table 5**). This knowledge has enabled the development of new cancer prevention strategies that use medicines and vaccines to eliminate or prevent infection with these agents. One of the best examples of this relates to human papillomavirus (HPV), which is estimated to have been responsible for almost 39,000 new cases of cancer in the United States in 2010 and more than 9,500 deaths (31).

Several decades of research have established that persistent infection with certain strains of HPV causes most, if not all, cervical cancers, a majority of anogenital cancers, and many cancers arising in the upper part of the neck (32). This information enabled the development of a clinical test for detecting the cancer-causing types of HPV. This test, when combined with a standard Pap test for cervical cancer, more effectively identifies women at high risk for cervical cancer than a standard Pap test alone. As a result, this test safely extends cervical cancer screening intervals (33), providing a less-burdensome cervical cancer screening option and potentially reducing health care costs.

Determining which strains of HPV can cause cervical cancer also led to the development of two vaccines that the FDA has approved for the prevention of cervical cancer (31, 34). In addition, the FDA approved one of the vaccines, Gardasil,

**Table 5: Infectious Causes of Cancer**

Bacteria	
Infectious Agent	Cancer
<i>Helicobacter pylori</i>	Stomach cancers
Parasites	
Infectious Agent	Cancer
<i>Clonorchis sinensis</i>	Biliary cancer, pancreatic cancer, and gallbladder cancer
<i>Opisthorchis viverrini</i>	Biliary cancer, pancreatic cancer, and gallbladder cancer
<i>Schistosoma haematobium</i>	Bladder cancer
Viruses	
Infectious Agent	Cancer
Epstein-Barr Virus (EBV)	Stomach cancers, Hodgkins and non-Hodgkins lymphomas, and nasopharyngeal cancers
Hepatitis B/C Virus (HBV and HCV)	Hepatocellular carcinoma
Human Immunodeficiency Virus (HIV)	Kaposi's sarcoma and non-Hodgkin's lymphoma
Human Papillomavirus (HPV)	Cervical, anogenital, head and neck, and oral cancers
Human T-cell Lymphotropic Virus, type 1 (HTLV-1)	T-cell leukemia and lymphoma
Merkel Cell Polyomavirus (MCV)	Skin cancer

## HPV Vaccine Usage

The Centers for Disease Control and Prevention (CDC) tracks vaccination coverage in the United States. It reported that in 2012 (35):

- Almost 54 percent of girls aged from 13 to 17 had received one dose of HPV vaccine.
- Just 33 percent of girls in this age group had received the recommended three doses of HPV vaccine.
- Of the girls who began the HPV vaccine series, almost 40 percent did not receive all three doses.

In addition, the CDC reported (37) that in 2010:

- Completion of the three-dose HPV series was lower among blacks and Hispanics than whites.
- Health insurance coverage for three doses of HPV vaccine was lower for those living below poverty.
- Poor and minority teens were less likely to receive all three recommended doses of the HPV vaccine.
- Fewer than 2 percent of males aged from 13 to 17 had received at least one dose of HPV vaccine.

Despite the low vaccine uptake, a recent report indicated that cervical infection with the strains of HPV targeted by the vaccines has decreased by 56 percent among females aged from 14 to 19 since the vaccine was introduced in 2006 (36).

### Change in Death Rates for CERVICAL CANCER (1990-2009)

**37.4%**



EST. 2013 INCIDENCE = 12,340 • DEATHS = 4,030

## Sleep Disturbances and Cancer

There is accumulating scientific evidence that qualitative and quantitative sleep disturbances increase a person's risk for developing cancer. Moreover, it appears that sleep disturbances increase cancer risk directly and indirectly through their link to obesity and type 2 diabetes.

Reports that shift workers have a higher incidence of breast, colorectal, prostate, and endometrial cancers support the link between sleep disturbances and cancer (38-41). Further evidence to support this link comes from two studies that indicate that short sleep duration and frequent insomnia increase postmenopausal women's risks for colorectal and thyroid cancers, respectively (42, 43).

In addition, recent studies indicate that sleep apnea, which is a well-established risk factor for cardiovascular mortality, is also linked with increased cancer mortality (44).

Research indicates that there are multiple ways in which sleep disturbances may influence the development of cancer. One indirect way is that sleep disturbances increase a person's chances of being obese and having type 2 diabetes (45, 46), both of which increase cancer risk. More directly, sleep disturbances may increase cancer risk as a result of the disruptions to an individual's circadian rhythm (47); decreases in melatonin levels (48); and disturbances in DNA repair processes (49, 50). Research into the role of circadian rhythms and disease is an active area of current investigation.

A recent study showed that close to a third of full-time workers in the United States get six or fewer hours of sleep each night (45). Sleep disturbances are, therefore, likely to become a significant contributor to cancer incidence. Clearly, more work is needed to completely understand the causes and develop potential interventions for this underappreciated cancer risk factor.

Moreover, it is becoming increasingly clear that cancer incidence and outcomes are profoundly affected by excess energy reserve accumulation. Importantly, many of the factors that lead to this accumulation and the consequences of this accumulation — including obesity, diabetes, metabolic syndrome, and inflammation — can be corrected by changing personal behaviors (51). Thus, restoring energy balance has the potential to reduce an individual's risk of developing cancer and improve outcomes for individuals already diagnosed with the disease.

It seems likely, however, that a multipronged approach will be required to disrupt the link between excess energy reserve accumulation and cancer because behavior change is challenging for many individuals, for many reasons. As we discuss below, a promising area of research in this context seeks to understand how factors affecting energy balance influence cancer development and outcome (51, 52).

for the prevention of vulvar and vaginal precancerous lesions as well as for the prevention of HPV-associated anal cancer. Future studies will determine whether the vaccines also reduce the risk for head and neck cancers caused by HPV. Early signs are promising, as a recent study found that vaccination dramatically reduced oral infection with HPV (34).

Even though two highly effective vaccines are available, the CDC estimates that in 2012 only 33 percent of girls in the United States aged 13 to 17 years had received the recommended three doses of HPV vaccine (35) (see sidebar on **HPV Vaccine Usage**, p. 23). Moreover, coverage has been reported to be significantly lower among the uninsured and in several states in which cervical cancer rates are highest and recent Pap testing prevalence is the lowest (33). However, recent data indicate that despite the low vaccine uptake, there has been a dramatic reduction in cervical infection with HPV among girls aged 14 to 19 years since the introduction of the vaccines (36). Thus, research has provided the tools for dramatic reductions in the burden of HPV-related cancers, but their use must be fully implemented if they are to have maximum impact.

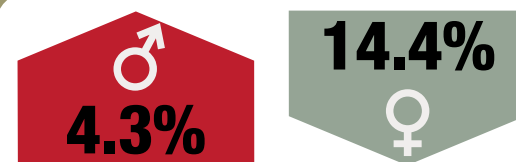
### Energy Balance: Weighing in on Cancer

“Energy balance” refers to the difference between the number of calories consumed and the number burned. Tipping of this balance so that a person accumulates excess energy reserves plays a crucial role in promoting the diseases responsible for the majority of deaths in the United States: heart disease and cancer.

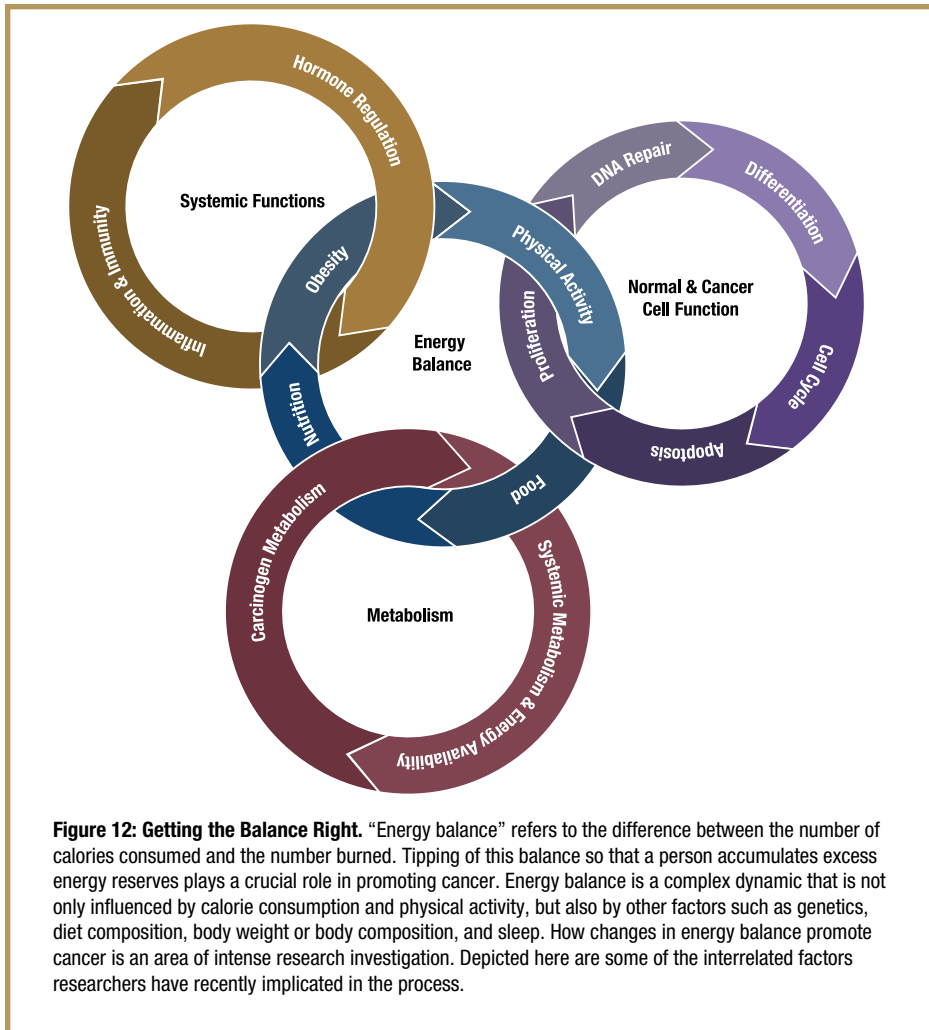
While calories are consumed only through eating and drinking, they are burned in many ways. Simply existing, breathing, digesting food, and pumping blood around the body use some calories. Added to these expenditures are the calories burned through a person's daily routine; the more physical activity in a routine, the more calories are burned.

Although this may seem straightforward, research has shown that energy balance is, in fact, a complex dynamic (see **Figure 12**). It is not only influenced by calorie consumption and

### Change in Death Rates for ESOPHAGEAL CANCER (1990-2009)



EST. 2013 INCIDENCE = 17,990 • DEATHS = 15,210



physical activity, but also by numerous other factors including genetics, diet composition, body weight, or body composition, and sleep (see sidebar **on Sleep Disturbances and Cancer**, p. 24).

**Obesity and Cancer**

Obesity increases risk for a growing number of cancers, most prominently the adenocarcinoma subtype of esophageal cancer, and colorectal, endometrial, kidney, pancreatic, and postmenopausal breast cancers (8). It also negatively impacts tumor recurrence, metastasis, and patient survival for several types of cancers (51, 53, 54).

How, then, does obesity promote and adversely affect survival for certain cancers? Several recent scientific discoveries have identified just some of the interrelated factors through which obesity influences cancer (46, 51, 52) (see **Figure 12**). Among these factors are hormones such as estrogen and insulin, which directly influence cell survival and division, and chemicals released by the fat itself, which influence the function of many organs of the body. In addition, obesity leads to inflammation, which is clearly linked to cancer development and progression (14, 55) (see **The Immune System**, p. 15).

Importantly, identifying some of the factors that link obesity and cancer is providing potential targets for treating obesity-related cancers. For example, the knowledge that several of the factors discovered act

**Sunbeds**

Did you know that **sunbed use** before the age of 35 almost doubles your risk of melanoma (26)

**How Do Physicians Know if I am Obese?**

Body mass index (BMI), which is calculated as weight in kilograms divided by height in meters squared, is used to define healthy weight, overweight, and obesity. In adults:

**BMI of 18.5–24.9 kg/m<sup>2</sup>** is considered healthy weight;

**BMI of 25.0–29.9 kg/m<sup>2</sup>** is considered overweight; and

**BMI of ≥30 kg/m<sup>2</sup>** is considered obese.

In children and adolescents, the definitions of overweight and obese are based on the 2000 CDC BMI-for-age-and-sex growth charts:

**BMI of ≥85th percentile to <95th percentile** is considered overweight; and

**BMI ≥95th** is considered obese.

## Change in Death Rates for UTERINE CANCER (1990-2009)

3.9%



EST. 2013 INCIDENCE = 49,560 • DEATHS = 8,190

directly on cancer cells to drive their survival and division via a signaling network called the PI3K/AKT/mTOR (46, 51, 52), suggests that drugs targeting this pathway might be effective in this context.

Any new therapeutic approaches developed in the future will need to be used together with approaches to balancing energy intake and output. For many people, modifying behaviors to reduce calorie consumption and increase physical activity may be sufficient, but other people may require surgical or therapeutic interventions to help them lose weight. The urgent need for an effective and comprehensive strategy is highlighted by the fact that the number of Americans classified as obese is at an all-time high. Currently, more than 35 percent of adults and 17 percent of children and adolescents are obese (56).

### ***Type 2 Diabetes Mellitus and Cancer***

Type 2 diabetes mellitus is a complex medical condition caused by a combination of factors, including obesity. Independent of obesity, type 2 diabetes increases an individual's risk of developing cancer (57, 58). Those with type 2 diabetes are most at risk for developing liver, pancreatic, and endometrial cancers, but also have an increased risk for developing biliary tract, bladder, breast, colorectal, esophageal, and kidney cancers, as well as certain forms of lymphoma (58, 59).

Type 2 diabetes not only increases cancer risk, but also reduces short- and long-term cancer survival rates through both direct and indirect mechanisms (58). For example, type 2 diabetes has been reported to have a direct negative effect on tumor recurrence and survival in patients with colon cancer (60). In general, survival for cancer patients with type 2 diabetes is worse than for their nondiabetic counterparts because of indirect factors associated with diabetes. For example, they are more likely to suffer from other potentially fatal diseases, like heart disease, and to be poor candidates for surgery and the highest doses of chemotherapy (58).

Despite the fact that type 2 diabetes affects about 7.5 percent of the U.S. population (61), it is not well established how type 2

diabetes increases cancer risk. Research suggests that it likely influences cancer development in several ways, many of which are similar to the ways in which obesity affects cancer (58, 59). For example, similar to obesity, type 2 diabetes increases levels of insulin and causes persistent inflammation.

Importantly, recent evidence suggests that treatments directed at reducing the hallmark of type 2 diabetes may influence cancer risk. Metformin, which is one of the most commonly used drugs for treating patients with type 2 diabetes, appears to reduce a type 2 diabetic's risk of developing colon and pancreatic cancers (62, 63). In contrast, sulfonylureas, a different class of drugs commonly used to treat type 2 diabetes, may increase risk of cancer development (58). However, further studies are needed to clarify these issues (58). Given what we have learned about the anticancer effects of metformin in patients with type 2 diabetes, numerous clinical studies are underway to assess whether it has the potential to benefit nondiabetic patients with cancer (64).

In light of the large number of Americans living with type 2 diabetes (61), it is critical for physicians managing these patients to be keenly aware of their patients' increased cancer risks if we are to reduce the burden of cancer in this portion of the population. Moreover, it is vital that we undertake more research so that we better understand the biological pathways linking the disease to cancer. Armed with this knowledge, we can investigate potential new therapeutic approaches. However, our best approach to reducing individuals' risks for type 2 diabetes and for certain forms of cancer, as well as improving outcomes, is to combine any new therapeutic approaches with behavior modifications, like eating a healthier diet, increasing physical activity, and reducing calorie consumption.

### ***Physical Activity and Cancer***

A lack of regular physical activity (see sidebar on **Physical Activity Guidelines**, p. 27) is strongly associated with an increased risk for colon, endometrial, and postmenopausal breast cancers, independent of weight (8). Mounting evidence suggests that it may also be associated with lung, pancreatic, and premenopausal breast cancers (8).

In addition, several recent studies indicate that sedentary behavior may increase risk for developing certain cancers and for mortality in cancer survivors independent of physical activity and weight.

For example, one study showed that individuals who spent 10 or more years in sedentary work had almost twice the risk of cancers arising in their rectum or in a specific part of their

## Physical Activity Guidelines

The U.S. Department of Health and Human Services issues the *Physical Activity Guidelines for Americans*, which provides science-based guidance to help Americans aged 6 and older improve their health through appropriate physical activity. The most recent version of the guidelines was published in 2008.

### Key Guidelines for Children and Adolescents

- Children and adolescents should do 60 minutes or more of physical activity daily.
- Most of this time should be either moderate-to-vigorous-intensity aerobic physical activity like running, and should include vigorous-intensity physical activity at least three days a week.
- Muscle- and bone-strengthening exercises like pushups or jumping rope, respectively, should be a part of daily physical activity and occur at least three days of the week.

### Key Guidelines for Adults

- All adults should avoid inactivity. Some physical activity is better than none, and adults who participate in any amount of physical activity gain some health benefits.
- Adults should undertake at least 150 minutes a week of moderate-intensity activity like a brisk walk, or 75 minutes a week of vigorous-intensity aerobic physical activity like running, or an equivalent combination of the two. Aerobic activity should be performed for at least 10 minutes at a time, and be spread throughout the week.
- Ideally, adults should increase their aerobic physical activity to 300 minutes a week of moderate intensity, or 150 minutes a week of vigorous-intensity, aerobic physical activity, or an equivalent combination of the two.
- Adults should also undertake muscle-strengthening activities that are moderate or high intensity and involve the legs, hips, back, abdomen, chest, shoulders, and arms on two or more days a week.

For older adults, those who are pregnant, and or those with disabilities, these guidelines are modified; see <http://www.health.gov/paguidelines/guidelines/summary.aspx> for further details.

For cancer survivors, it is recommended that they follow the *2008 Physical Activity Guidelines for Americans* with specific exercise programming adaptations based on disease and treatment-related adverse effects (65, 66).

colon compared with individuals who did not spend any time in sedentary work (67). In a second study, patients with colorectal cancer who spent six or more hours a day sitting after their diagnosis had a dramatically increased risk of death from their cancer compared with patients who spent fewer than three hours a day sitting (68). Likewise, a large-scale study also showed that the more time a person spent sitting, the greater their risk of death from any cause, regardless of their level of physical activity (69).

Conversely, research has shown that for patients with certain forms of cancer, including breast, colorectal, and prostate cancers, physical activity improves outcomes by reducing recurrence and increasing survival (8, 70-73).

Clear guidelines for physical activity for cancer survivors have been published (8, 65, 66). However, it appears that these have mostly been applied in clinical settings and research interventions, and that they have not yet become general standards of practice in the United States.

There are many barriers to increasing physical activity among cancer survivors and the general public. More research and resources at all levels are needed if this lifestyle modification is to be widely adopted.

## Looking For Cancer: Who, When, and Where

We know that most cancers arise from genetic mutations that have accumulated during the patient's lifetime (see **Developing Cancer**; p. 17). Our knowledge of the causes, timing, sequence, and frequency of these pivotal changes is increasing, as is our insight into the specific implications of the changes. This knowledge provides us with unique opportunities for developing the means to prevent cancer onset or to detect it and intervene earlier in its progression.

Unfortunately, we have also learned that it is not always easy to identify at-risk patients or those with early-stage disease. However, researchers and clinicians are looking to pair our molecular understanding of cancer development with indicators of cancer risk to create personalized prevention and early-stage intervention programs. For example, some patients may be able to reduce their risk by simply 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 precautionary surgery (see **Tables 6 and 7**, pp. 28 and 30, respectively).

## How do I Know if I am at High Risk for Developing an Inherited Cancer?

If, in your family there is/are:

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

Adapted from: <http://www.cancer.org/Cancer/CancerCauses/GeneticsandCancer/heredity-and-cancer>.















## Classifying Risk

### Prevention and Early Detection of Primary Tumors

About 5 percent of all new cases of cancer diagnosed in the United States each year are caused by an inherited mutation (1) (see sidebar on **How do I Know if I am at High Risk for Developing an Inherited Cancer?**). In most of these cases the inherited mutation is unknown. However, research has identified 17 mutations that put people, like **Congresswoman Wasserman Schultz**, at very high risk of developing cancer (see **Table 8**, p. 31). If a patient's cancer is suspected to be caused by one of these mutations, genetic testing can be performed to verify this and identify relatives who carry the familial mutation. These family members can then consider taking risk-reducing measures, while those without the mutation can avoid unnecessary and costly medical procedures.

Beyond inherited cancers, a number of medical conditions place an even smaller group of individuals at high risk for developing certain types of cancer. Among these medical conditions are ulcerative colitis and Crohn's disease, which are chronic inflammatory diseases of the intestines that increase an individual's risk for colorectal cancer sixfold (74). Moreover, medical conditions and interventions that suppress the normal function of the immune system, such as HIV/AIDS and the treatment of solid organ transplantation with immunosuppressive drugs, also increase risk for certain types of cancer (75).

**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.

## The Honorable Debbie Wasserman Schultz

Age 47  
Weston, Fla.

Breast Cancer Survivor Since 2007



For as much as I knew as an advocate in the fight against breast cancer over my 20-year legislative career, I quickly realized in late 2007 that there was much I didn't know when I found a lump just six weeks after a clean mammogram — it was breast cancer, and I was only 41. At the time, I did not know that as an Ashkenazi Jew, I was five times more likely to have the BRCA 1 or BRCA2 gene mutation. I did not know that carriers of the BRCA gene mutations have up to an 85 percent lifetime chance of getting breast cancer and up to a 60 percent chance of getting ovarian cancer. I found out that I do have the BRCA2 mutation. I was fortunate that I found the tumor early, but I didn't find my tumor through luck. I found it through knowledge and awareness.

It was also made plainly clear to me that despite the perception that breast cancer is something older women need to worry about, young women can and do get breast cancer. Sharing this knowledge is critical because young women's breast cancers are generally more aggressive, are diagnosed at a later stage, and result in lower survival rates. One reason they are diagnosed at a later stage is because many young women simply don't think they can get breast cancer. And even if they do suspect something is wrong, too many physicians dismiss their concerns because they also believe that the woman is simply too young to have breast cancer.

After experiencing the importance of early detection firsthand, I knew that I had to introduce legislation to help other young women facing this terrible disease. That is why, as soon as I was cancer-free, I introduced the Breast Health Education and Awareness Requires Learning Young Act, or the EARLY Act. I'm proud to report that the EARLY Act became law in 2010 as part of the Affordable Care Act and is already being implemented.

The EARLY Act focuses on a central tenet: that we must empower young women to understand their bodies and speak up for their health. It creates an education and outreach campaign that highlights the breast cancer risks facing women 45 and under, and empowers them with the tools they need to fight this deadly disease. It helps educate and sensitize health care providers about the specific threats and warning signs of breast cancer in younger women that lead to early detection, diagnosis, and survival.

Looking to the future, I am committed to finding those gaps in cancer treatment and awareness and working on legislative solutions to fill those voids. I think of all the women who have fought the breast cancer battle as my sisters in survival, united and made that much stronger by these difficult experiences. I could not be more grateful to everyone who has chosen to join us in this fight, so that we can support each other, and eliminate cancer, once and for all.



**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

## USPSTF Cancer Screening Guidelines

The U.S. Preventive Services Task Force (USPSTF) is an independent group of experts that makes evidence-based recommendations about clinical preventive services such as screenings, counseling services, or preventive medications. Importantly, recommendations can be revised if research uncovers new evidence.

The USPSTF has made numerous recommendations related to population-based screening for early detection of several cancers. Here we highlight its recommendations, as of Aug. 1, 2013, for generally healthy individuals.

- Breast cancer:
  - ❖ For women aged 50 to 74 years, screening mammography once every two years.
  - ❖ For women younger than 50, the decision to start regular screening should be an individual one.
- Cervical cancer:
  - ❖ For women aged 21 to 29 years, a Pap test every three years.
  - ❖ For women aged 30 to 65 years a Pap test every three years or a Pap test and human papillomavirus (HPV) testing every five years.
- Colorectal cancer:
  - ❖ For adults aged 50 to 75 years, fecal occult blood testing, sigmoidoscopy, or colonoscopy.
- Draft lung cancer recommendation:
  - ❖ For adults aged 55 to 79 years, annual low-dose computed tomography for those who have smoked one pack per day for 30 years or equivalent (two packs per day for 15 years, etc.).

Not listed are the screening programs the USPSTF believes there is insufficient evidence to recommend for or against (e.g., screening for ovarian cancer).

However, high-risk individuals are the minority, so what is to be done for the broader population? One approach to identifying at-risk patients, as well as those with early-stage disease, is to test generally healthy individuals for potential disease through population-based screening programs (see sidebar on **USPSTF Cancer Screening Guidelines**). These programs largely function by using age and gender to grade, or stratify, a person's risk, with those identified as most at risk being those who are most likely to benefit from the screening.

This approach to risk stratification has been extremely successful for cervical cancer screening, as the program has greatly reduced the incidence and mortality of cervical cancer in the United States (76, 77). Further inroads against cervical cancer incidence are likely given the dramatic reduction in cervical infection with the cervical cancer-causing infectious agent HPV among girls aged 14 to 19 years since the introduction of the HPV vaccines (36).

Stratifying risk based on age has also worked for colonoscopy, which has contributed significantly to dramatic declines in colorectal cancer incidence and mortality (38). However, only about 59 percent of all Americans aged 50 years and older, the group for whom colorectal cancer screening is currently recommended, get screened (78). Among the more than one-third of Americans who do not follow colorectal cancer screening guidelines is a disproportionately high number of African-Americans (78, 80), a group that shoulders an overly high colorectal cancer burden (see sidebar on **Cancer Health Disparities in America**). Evidently, innovative ways to increase the number of individuals, in particular racial and ethnic minorities, following colorectal cancer screening guidelines are needed.

### Change in Death Rates for COLON AND RECTUM CANCER (1990-2009)

38.1%



35.7%



EST. 2013 INCIDENCE = 142,820 • DEATHS = 50,830

## 70% Decrease

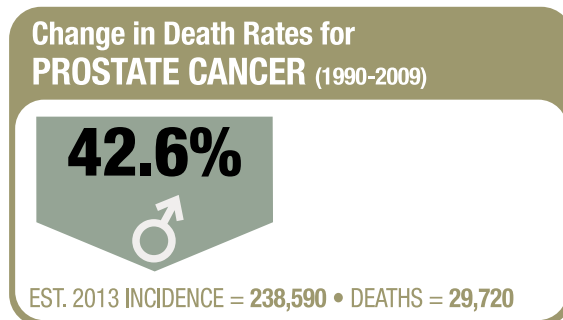
There was a **70 percent decrease** in cervical cancer deaths from 1955 to 1972, largely as a result of the Pap test (31).

Since 2003, a spectacularly successful initiative at eliminating colorectal cancer disparities has been running in Delaware (81). The cancer control program, as it is known, increased colorectal cancer screening among all Delawareans age 50 or older from 57 percent in 2002 to 74 percent in 2009. Moreover, screening rates for African-Americans rose from 48 percent to 74 percent, matching the screening rate among non-Hispanic whites for the same period of time. Perhaps most importantly, disparities in colorectal cancer incidence and mortality rates between non-Hispanic whites and African-Americans were also equalized as a result of the equivalent screening rates between the two groups. The researchers who conducted this study predict that if similar programs could be implemented in all states, racial disparities in colorectal cancer incidence and mortality could be greatly reduced (81).

Screening programs have successfully reduced the incidence and mortality for cervical and colorectal cancers because they identify the diseases at an early-stage before they become life threatening, thereby providing opportunities for early

intervention. However, not all population-based screening programs have been equally effective.

For example, while the prostate-specific antigen (PSA) test is very good at detecting early-stage prostate cancer lesions, it does not distinguish between lesions that will progress to advanced disease and those that will not (88). As a result, many patients undergo unnecessary treatment. Concerns about overdiagnosis and overtreatment have led to the current



**Table 8: Inherited Cancer Risk**

Cancer	Syndrome	Associated Gene
Leukemias and lymphomas	Ataxia telangiectasia	<i>ATM</i>
All cancers	Bloom syndrome	<i>BLM</i>
Breast, ovarian, pancreatic, and prostate cancers	Breast-ovarian cancer syndrome	<i>BRCA1, BRCA2</i>
Breast, thyroid and endometrial cancers	Cowden syndrome	<i>PTEN</i>
Colorectal cancer	Familial adenomatous polyposis (FAP)	<i>APC</i>
Melanoma	Familial atypical multiple mole–melanoma syndrome (FAMM)	<i>CDKN2A</i>
Retinal cancer	Familial retinoblastoma	<i>RB1</i>
Leukemia	Fanconi’s anemia	<i>FACC, FACA</i>
Colorectal cancer	Hereditary nonpolyposis colorectal cancer/Lynch syndrome	<i>MLH1, MSH2, MSH6, PMS2</i>
Pancreatic cancer	Hereditary pancreatitis/familial pancreatitis	<i>PRSS1, SPINK1</i>
Leukemias, breast, brain and soft tissue cancers	Li-Fraumeni	<i>TP53</i>
Pancreatic cancers, pituitary adenomas, benign skin and fat tumors	Multiple endocrine neoplasia 1	<i>MEN1</i>
Thyroid cancer, pheochromocytoma	Multiple endocrine neoplasia 2	<i>RET, NTRK1</i>
Pancreatic, liver, lung, breast, ovarian, uterine and testicular cancers	Peutz–Jeghers syndrome	<i>STK11/LKB1</i>
Tumors of the spinal cord, cerebellum, retina, adrenals, kidneys	von Hippel-Lindau syndrome	<i>VHL</i>
Kidney cancer	Wilms’ tumor	<i>WT1</i>
Skin cancer	Xeroderma pigmentosum	<i>XPD, XPB, XPA</i>

## Colorectal Cancer Screening

If the proportion of individuals following **colorectal cancer screening** guidelines increased to slightly more than 70 percent, researchers estimate that 1,000 additional lives per year could be saved (79).

## Cancer Health Disparities in America

Cancer health disparities are differences in the incidence, treatment, and outcomes of cancer that exist among specific populations in the United States. These populations are often racial and ethnic minority groups, but can also include individuals with low socioeconomic status, residents in certain geographic locations, the elderly, and individuals from other medically underserved groups. Differences in access to healthcare and healthy foods, behavioral factors, and health literacy are well-documented causes of disparities, but genetic, environmental, and social and cultural factors, including those that can negatively alter the relationship between patients and health care providers, contribute to disparities as well.

Research plays a key role in the identification of disparities and in the untangling of their complex and interrelated causes, ultimately leading to the development of effective interventions. An example of an evidence-based intervention is Delaware's cancer control program (see **Prevention and Early Detection of Primary Tumors**, p. 28), which eliminated colorectal cancer disparities between African-Americans and non-Hispanic whites through the creation of a comprehensive statewide screening program that included coverage for screening and treatment and patient navigators to help guide patients through the screening, treatment, and follow-up processes (81).

The Delaware initiative is a success story, but unfortunately new interventions, including new therapeutics, are not always adequately tested in all of the populations that could benefit from them. For example, racial and ethnic minorities are significantly under-represented in cancer clinical trials. This means that therapies may be approved with little evidence as to their effect in minority populations. In an effort to address this potential source of disparities, several federal agencies, including the U.S. Food and Drug Administration (FDA) and the National Institutes of Health (NIH), have been working to increase minority representation in clinical trials, and a number of independent advocacy efforts have also been launched to address hurdles to minority participation in clinical research.

The demographic changes that are anticipated over the next few decades highlight the importance of addressing cancer health disparities in America. By 2050, it is expected that 30 percent of the

population will be Hispanic and 15 percent will be African-American (5, 82). Cancer is already the leading cause of death for Hispanics, accounting for approximately 21 percent of deaths overall and 15 percent of deaths in children, and African-Americans are more likely to die from cancer than any other racial group (1, 5). Therefore, the future health of these groups, and all Americans facing cancer, will require the continued generation of new insights into the underlying causes of cancer health disparities, and the implementation of effective interventions for the elimination of those disparities.

The causes of disparities are complex and interrelated, making it difficult to isolate and study the relative contribution of each. However, below are a few examples of factors that have been shown to play a strong role in differences in cancer incidence and mortality.

**Differences in Treatment:** For example, only 60 percent of African-Americans diagnosed with early-stage lung cancer are likely to receive recommended surgical resection compared with 76 percent of their white counterparts. African-Americans correspondingly suffer a 25 percent greater mortality in lung cancer (83, 84).

**Genetics:** For example, the incidence of breast cancer in Hispanic women is nearly 30 percent less than for non-Hispanic whites, but research has found that the more European ancestry Hispanic women have, the more likely they are to develop breast cancer (5, 85).

**Environment/behavior:** For example, stomach cancer incidence in Japanese Americans is less than half that of Japanese who reside in Japan, showing how changed environment can affect cancer risk (12, 86).

**Access to Healthcare:** For example, Hispanic women are 1.5 times more likely to die of cervical cancer than non-Hispanic whites. The cervical screening rate among uninsured Hispanic women is only 53 percent compared to 63 percent for uninsured non-Hispanic whites. Hispanics are uninsured at a rate over 2.5 times that of non-Hispanic whites (41 percent versus 15 percent) (5, 87).

recommendation by a number of organizations to discontinue routine PSA screening (89) and highlight the need for better ways to stratify PSA-positive patients.

Early detection of breast cancer through regular mammography screening of women older than 40 has been credited with reducing the mortality rate for breast cancer (1). However, there is growing concern that it can detect breast tumors that will never cause symptoms or threaten a woman's life. Thus, mammography screening, like PSA screening, can potentially lead to overdiagnosis of the disease and subsequent overtreatment, which carries its own risks. In fact, one study estimated that in 2008, breast cancer was overdiagnosed in more than 70,000 women; this accounted for 31 percent of all breast cancers diagnosed (90).

One approach to more precisely identify at-risk patients is to use their history. In a study investigating the usefulness of low-dose computed tomography (CT) screening for early detection of lung cancer, current and former heavy smokers aged 55 to 74 years were classified as having the highest risk for developing disease (91, 92). The researchers found that in this population, low-dose CT screening reduced lung cancer mortality by 20 percent because it identified small and early-stage tumors (91, 92). There are an estimated 94 million current and former smokers in the United States; however, the majority of them are unlikely to benefit from screening because they are or were not heavy smokers (93).

More work is needed to ensure that Americans understand that cancer screening approaches, including low-dose

## Change in Death Rates for LUNG & BRONCHIAL CANCER (1990-2009)

32.0%



4.8%



EST. 2013 INCIDENCE = 228,190 • DEATHS = 159,480

CT screening for early detection of lung cancer, are most clinically effective when targeted at those at highest risk of developing the disease for which they are being screened (94). Targeting those most at risk also has the benefit of decreasing the complications and cost of unnecessary health care interventions for those at low risk of disease. Research to develop new, accurate, and reliable ways to discern an individual's cancer risk is vital to ensure that the public has

confidence in current screening guidelines and any future changes to these guidelines.

### *Prevention and Detection of Tumor Recurrence*

As for prevention and early detection of primary tumors, our increasing knowledge of the risk factors for cancer occurrence and progression is enabling us to identify those cancer survivors with the highest risk for tumor recurrence (see sidebar on **Cancer Survivorship**). This is allowing us to direct risk-reducing medical interventions to only those who will benefit, reducing health care costs associated with treating those who will not benefit and may even be harmed.

Currently, there are few established ways to identify cancer survivors at high risk for disease recurrence. One group known to be at high risk is women who have successfully completed treatment for invasive breast cancer. A subset of patients in this group has breast cancer powered by the hormone estrogen. For these women, drugs that block the effects or

## Cancer Survivorship

According to the National Cancer Institute (NCI), a cancer survivor is anyone living with, through, or beyond a cancer diagnosis. While we use the term "cancer survivor" here in this report, it is important to note that not all people with a cancer diagnosis identify with it.

As a result of advances in cancer research more people are surviving longer and leading fuller lives after their initial cancer diagnosis. In fact, the number of cancer survivors living today in the United States is estimated to have risen to more than 13.7 million, which is approximately 4 percent of our nation's population (2).

This is a growing population; in fact, it is estimated that the number of cancer survivors in the United States will reach 18 million by 2022 (2). This expansion can be attributed to numerous factors including earlier cancer detection, which increases the chance for curative treatment; more effective and less toxic treatments, particularly for advanced and metastatic disease; and the aging and growing population.

Also increasing is long-term survivorship. However, survivorship rates vary considerably depending on cancer type, patient age at diagnosis, and other characteristics. In the United States in 2012, an estimated 64 percent of survivors were diagnosed with cancer five or more years ago, and 15 percent were diagnosed 20 or more years ago (2). Among children diagnosed with cancer, the chances of long-term survival are even greater: three out of every four American children receiving a cancer diagnosis are alive 10 or more years later (95).

There are at least three distinct phases associated with cancer survival, each accompanied by its own unique set of challenges. These phases include the time from diagnosis to the end of initial treatment, the transition from treatment to extended survival, and long-term survival. Here, we focus on the issues facing long-term cancer survivors, which vary depending on the age of the survivor.

While some cancer survivors experience few, if any, health-related challenges, many suffer serious and persistent adverse outcomes. Some of these effects may start during cancer treatment and continue long term, but others can appear months or even years later. These long-term and late effects may be emotional and/or physical. For example, cancer survivors are at increased risk for anxiety and depression as well as damage to the heart, lungs, and kidneys, cognitive impairment, and infertility.

Further, many survivors live in fear that their cancer will return at some point. In fact, cancer survivors are at risk for recurrence of the original cancer and for the development of a new, biologically distinct, second cancer, with risk dependent on the original type of cancer, stage of disease at diagnosis, and treatments received.

The almost 60,000 pediatric cancer survivors (aged from 0 to 14 years) estimated to be living in the United States often face an increased risk of serious negative long-term and late effects as a result of treatments received while their bodies are still developing (2). Adolescents (ages 15 to 19 years) and young adults (ages 20 to 39 years) also have to confront a distinctive set of concerns, including adapting to long-term cancer survivorship while beginning careers and thinking about families of their own.

It is clear that a person diagnosed with cancer may be faced with critical problems that diminish their quality of life for many years. Thus, a new focus for cancer research is to help the increasing number of cancer survivors achieve a higher quality of life by avoiding or diminishing the potential long-term and late effects of successful treatments. By gaining a better understanding of these issues confronting cancer survivors, the cancer research and advocacy community can continue to play an integral role in meeting the needs of survivors, their loved ones, and future Americans navigating the cancer journey.

production of estrogen have proven very successful at reducing tumor recurrence if taken for five years (96-98) (see **Table 6**, p. 28). Moreover, recent data from long-term clinical trials indicate that 10 years of therapy with one of these drugs, tamoxifen (Nolvadex), is even more effective at reducing tumor recurrence (99, 100). As all anti-estrogen drugs have serious side effects, our knowledge that these drugs are ineffective for women whose breast cancers are not fueled by estrogen spares these patients from unnecessary and potentially harmful treatments.

Recent research has identified a potential new way to target treatment that reduces tumor recurrence to only those cancer survivors likely to benefit (101). Prior research had indicated that regular aspirin use could lower risk of both primary and recurrent colorectal cancer (102, 103). However, widespread aspirin use was not recommended because of concerns over side effects such as gastrointestinal bleeding. Fortunately, researchers have been able to narrow down the population of colorectal cancer survivors who will benefit from aspirin (101). They found that regular aspirin use by colorectal cancer survivors with tumors harboring mutations in the PIK3CA gene reduced their risk of colorectal cancer death by about 80 percent, but that aspirin showed no benefit for survivors who lacked this mutation in their tumors.

This knowledge promises to reduce colorectal cancer morbidity and mortality for certain colorectal cancer survivors and to eliminate the needless treatment of those who will not benefit. However, additional, large-scale studies are needed before aspirin use can become a standard treatment for patients with PIK3CA-mutated colorectal tumors.

Despite these successes, the use of medical interventions to reduce primary and recurrent tumor risk is not widespread. Therefore, continued research is needed to develop more concrete evidence to identify the most at-risk patients, better screening approaches, and more and better ways to intervene earlier in the progression of cancer.

# Making Research Count for Patients: A Continual Pursuit

## In this section you will learn:

- Mobilizing a patient's own **immune system** to treat cancer is yielding **remarkable and durable responses**, making immunotherapy an exciting area of cancer research.
- From Sept. 1, 2012, to July 31, 2013, the FDA approved **11 new drugs** for treating cancers, eight of which are molecularly targeted drugs.
- During the same period of time, the FDA **approved new uses** for three previously approved anticancer drugs, one of which is a nanodrug.
- In addition, three **new technologies** that improve cancer detection or guide treatment were approved by the FDA.
- **Cancer genomics research** has led to clinical sequencing of tumors, which is beginning to guide cancer diagnosis and treatment.

Decades of cancer research have fueled extraordinary medical, scientific, and technical advances that gave us the tools that we now use for the prevention, detection, diagnosis, and treatment of cancer. Together, these advances have helped save millions of lives in the United States and worldwide. As highlighted in the **Special Feature on Immunotherapy**, p 38, one area that is beginning to revolutionize the treatment of certain cancers, and that holds incredible promise for the future, is immunotherapy.

It takes many years of dedicated work by thousands of individuals across the research community to bring a new drug, device, or technique from a concept to FDA approval. From Sept. 1, 2012, to July 31, 2013, this Holy Grail was achieved for 11 new drugs, three existing drugs with new uses, and three new imaging technologies, thereby accelerating the pace of progress in both cancer treatment and detection (see **Table 1**, p. 4). Two of these drugs were approved with companion diagnostics to ensure that only patients who are likely to benefit from the drugs, receive them.

It is important to note that most patients, like **Mary Jackson Scroggins** and **Congressman Fitzpatrick**, are not treated

with drugs alone but usually with some combination of surgery, radiotherapy, and chemotherapy (see **Appendix Tables 1 and 2**, p. 81). One new radiotherapeutic, radium-223 dichloride (Xofigo), was approved by the FDA for the treatment of prostate cancer that has spread to the bones in May 2013. This low-energy radioactive drug is the first of its kind to be approved by the FDA. It specifically delivers radiation to tumors in the bones, limiting damage to the surrounding tissues (104) (see **Table 1**, p. 4).

The following discussion focuses on recent FDA approvals as well as advances against cancer that are showing near-term promise.

### Change in Death Rates for OVARIAN CANCER (1990-2009)

**15.9%**



EST. 2013 INCIDENCE = 22,240 • DEATHS = 14,030

A portrait of Mary (Dicey) Jackson Scroggins, a woman with dark hair styled in braids, wearing a brown and white patterned top. She is looking directly at the camera with a slight smile. The background is a blurred green lawn.

## Mary (Dicey) Jackson Scroggins

Age 62  
Washington, D.C.

17-Year Ovarian Cancer Survivor  
and Advocate

I am a 17-year ovarian cancer survivor. The knowledge that my survival depended so heavily on chance and good luck fueled my desire to spread awareness about gynecologic cancers, cancer health disparities, and the need for more research funding.

I was 46 years old when I was diagnosed with stage 1a ovarian cancer. For about two years, I had experienced symptoms that could have suggested ovarian cancer — abdominal bloating, weight gain, frequent urination, and excessive menstrual bleeding. I know my body and knew something wasn't right, so I changed gynecologists during this period to find answers and get relief, but none of us ever suspected cancer.

To remove fibroid tumors and an ovarian cyst, I had a hysterectomy in September 1996. During the surgery, my gynecologist discovered the tumorous ovary and contacted a gynecologic oncologist to complete the surgery. In so doing, she probably saved my life and surely increased my chances of recurrence-free survival.

When my gynecologic oncologist called with the pathology report, he told me he had good and bad news. The good news was that I had stage 1a ovarian cancer, which is the earliest and most treatable stage. The bad news was that it was clear-cell, the most aggressive and least well understood ovarian cancer type.

Although my cancer was early-stage, primarily because it was clear-cell, I received six cycles of chemotherapy — paclitaxel (Taxol) and cisplatin (Platinol). The side effects from the chemotherapy were typical — slight nausea and fatigue for a few days after each cycle and hair, taste, and appetite loss — but overall, except for one bad reaction to anti-nausea medication, my treatment was pretty uneventful.

I finished chemotherapy in February 1997 and have not had a recurrence of the disease. For this I am truly thankful. And although I am still very careful about my health care, the frequency of my follow-up CT scans has decreased.

My oncology nurse, Alice Beers, was vital to my early recovery. She was also instrumental in connecting me with other women who had gynecologic cancers, and I joined the Ovarian Cancer National Alliance, which along with my family became a lifeline. The connection to survivors who understood the disease and who were active in helping others — even as they waged their own battles — was empowering.

Although I had always been active in my community, these connections sparked my advocacy efforts in the cancer community. And since I passionately believe that no one's survival and well-being should be driven by ZIP code, race or ethnicity, or socioeconomic status, one of the initiatives closest to my heart is the elimination of cancer health disparities. There is no acceptable level of the unnecessary and selective suffering and death experienced by medically underserved populations.

A powerful mechanism for reducing and ultimately eliminating cancer and other health disparities is research. As a matter of good science and of good conscience, that research must be anchored with clinical trials that include participants from all segments of the population.

We are all touched by cancer, and we must have the will as a nation to ensure that every citizen will receive the level, length, and depth of care that is appropriate for her or his condition. To do so, we must act on what we already know and on what we learn through research.

One of the reasons that I advocate for others and share my experience is to spread awareness that ovarian cancer can strike any woman, at any age, of any race, and that it is neither silent nor necessarily a death sentence.

## The Honorable Michael Fitzpatrick

Age 50  
Levittown, Pa.

Five-year Colorectal Cancer Survivor



At first, the symptoms were familiar — not disabling — not much to worry about. We pick up a virus now and then, it makes us sick for a few days, and it's over. But there was a day in spring 2008 when the “virus” had not subsided. The symptoms were even more pronounced by the time I relayed this to my wife. In retrospect, the symptoms were similar to what we know about colon cancer, but I chose to ignore them — I was having a couple of busy weeks.

It was obvious this was not a virus. At my wife's insistence, not my better judgment, I went to the doctor for screening and soon after I was told I had colon cancer — later learning it was stage 3.

There are many things I know now about recognizing symptoms, as well as family history. In my case, four grandparents died from cancer; both my parents are cancer survivors, and a sister.

My first thoughts on hearing the news: I was 44 years old, a father of six, seemingly in good health. Two words come to mind: *disbelief* and *incomprehensible*. Needless to say, life changed that day and I was forced to focus on my health and the future. Two other words came to mind: *cure* or *not*.

I began treatment at our local community hospital with a great team of physicians, nurses, and technicians administering chemotherapy and a “lifetime dose” of radiation. I was scheduled for four months of very aggressive treatment, beginning in June 2008, leading up to surgery scheduled for October that same year.

Following the mandatory, presurgery examination, I was surprised to learn that the tumor was gone — “melted away,” someone said. I had a choice to have the surgery, regardless, or just post-surgery chemotherapy. I opted for the latter. From October 2008 to March 2009, I underwent the prescribed treatment, and during this nine-month period of treatment at the hospital, I watched the health care bill being debated in Congress. At that point, it was personal.

I was often asked how I felt while undergoing treatment. I suppose it is different for each of us. I was tired, not feeling great most days, but I never missed a day at the law office. I even tried a case in court. Maybe it was a “life goes on” effort, but it worked.

With my illness in remission, I decided I should get back in the game, and in January 2010 I announced that I would run for my old congressional seat. I made the announcement in front of the hospital where I had been treated, with the port in my chest reminding me the cancer could return.

In the aftermath, I look at life knowing I've been given a second chance. Of course, I always appreciated my family, my wife and six kids, seven siblings, parents — but facing your own mortality somehow changes the view. What we take for granted, soars. I even decided to have another run at Congress — and regained my former seat.

In my chosen profession now, I believe this experience has made me a better advocate for the rights of citizens dealing with cancer. I am much more passionate about debating the need for additional money for cancer research so this disease can be thoroughly beaten.

Thus far, I've been spared, and I'm forever thankful to God and the wonderful care I received, and continue to receive, in follow-up visits. I have the utmost respect for those in the healing profession — the physicians and scientists who have chosen this path so others may live. They have my heartfelt gratitude.



# Special Feature on Immunotherapy

## Decades of Research Now Yielding Results for Patients

An important milestone for cancer research was the discovery that the immune system can identify and eliminate cancer cells the way it does disease-causing pathogens.

The study of the structure and function of the immune system is a field of research called immunology (see sidebar on **Key Players in the Immune System**). Tumor immunology (sometimes called cancer immunology) is the study of interactions between the immune system and cancer cells.

The immune system naturally eliminates some cancers before they become life threatening. Researchers, therefore, thought that it should be possible to develop therapies that would train a patient's immune system to destroy their cancer. Such therapies, referred to as immunotherapies, are now beginning to revolutionize the treatment of some cancers, yielding both remarkable and durable responses. Although getting to this point has proven challenging, the field holds immense promise, as discussed by cancer immunology pioneer **Drew Pardoll**.

Not all immunotherapies work in the same way. Some boost the natural cancer-fighting ability of the immune system by taking its brakes off, some increase the killing power of the patient's immune cells, and some flag cancer cells for destruction by the immune system.

Researchers studying the intricacies of the immune system are identifying novel immunotherapies and new ways to utilize those that we already have, including the potential for combining immunotherapies that operate in different ways or combining immunotherapies with either radiation therapy or other drugs. For example, it might be possible to design a combination treatment that releases the brakes on the immune system and simultaneously steps on the accelerator to enhance immune cells' killing power.

### Releasing the Brakes on the Immune System

Immune cells called T cells (see sidebar on **Key Players in the Immune System**) are naturally capable of destroying cancer cells; however, many tumors develop sophisticated ways to stop these T cells from functioning. One way this happens is that T cells in the tumor microenvironment display on their

## Key Players in the Immune System

White blood cells, or leukocytes, are the cells of the immune system that work together to protect the body from pathogens. Some can also recognize cancer cells as dangerous to the body and attack and destroy them. Here, we provide a very brief description of the unique functions of some of the white blood cells that have a central role in this process.

T cells, or T lymphocytes, are divided into two main types: those that have the protein CD4 on their surface (CD4<sup>+</sup> T cells) and those that have the protein CD8 on their surface (CD8<sup>+</sup> T cells). CD4<sup>+</sup> and CD8<sup>+</sup> T cells both "identify" their target through a groups of proteins on their surface called T-cell receptors.

CD8<sup>+</sup> T cells are sometimes called cytotoxic T cells or killer T cells. When they are called into action, they attack and destroy their targets.

CD4<sup>+</sup> T cells respond differently to CD8<sup>+</sup> T cells when called into action. They do not kill their targets, rather they orchestrate multiple other types of immune responses. For example, they release factors, or cytokines, that direct the function of other immune cells. CD4<sup>+</sup> T cells that produce the cytokines interleukin-12 and interferon- $\gamma$ , which help CD8<sup>+</sup> T cells function, are called T helper 1 cells, or Th1 cells.

A distinct subset of CD4<sup>+</sup> T cells keeps other immune cells in check, preventing them from attacking our own normal cells and from over responding to pathogens. These cells are called regulatory T cells, or Treg cells. Some cancers actively recruit Treg cells to help shut down the anticancer immune response.

B cells, or B lymphocytes, respond to pathogens and cancer by releasing factors called antibodies. Each B cell makes a single antibody. Monoclonal antibodies, one of the most important classes of anticancer therapy, are derived from the progeny of a single B cell selected to produce one antibody with high specificity for the therapeutic target of interest.

Dendritic cells have a central role as sentinels in the immune system. They alert T cells to the presence of disease-causing pathogens or cancer cells, triggering the T cells' responses.

Natural killer cells, or NK cells, macrophages, and neutrophils are additional specialized immune cell types that are some of the "first responders" of the immune system. When called into action, they release factors that kill their targets.

## Drew Pardoll, M.D., Ph.D.

Professor of Oncology, Director of Cancer Immunology  
The Sidney Kimmel Comprehensive Cancer Center  
at Johns Hopkins, Baltimore, Md.



Immunotherapy as a treatment for cancer is a dream that is more than 110 years old. But we have now reached an inflection point: in the past three years, a number of immunotherapies have emerged that work in different ways to achieve amazing, long-lasting responses that can be measured in years not months.

It all started in the 1890s, when William Coley noticed that the immune system's response to a bacterial infection seemed to spill over and cause tumor regression in some cancer patients. So, he began to treat his cancer patients by infecting them with certain kinds of bacteria. Although Coley reported some successes, his approach to cancer treatment was never widely adopted.

Since Coley's efforts, we have gained immense scientific insight into the pathways, molecules, and cells that regulate the immune system and execute its functions. Integrating this understanding of the immune system with our knowledge of the biology of cancer is beginning to allow us to intelligently design immunotherapies that are working for a significant number of patients.

This progress is very recent. Before 2010, which is when the FDA approved the first therapeutic cancer vaccine, sipuleucel-T (Provenge), for the treatment of prostate cancer, investigational immunotherapies would cause tumor regression in a few patients, but not enough patients for the immunotherapies to become established treatment options.

In the past, the development of immunotherapies called therapeutic cancer vaccines was plagued by failure in large phase III clinical trials despite some positive patient responses. But now that immunologists have gained more knowledge of the molecules and cells involved in activating the immune system, I believe that over the next three years, therapeutic cancer vaccines will become a core component of cancer immunotherapy combinations.

Therapeutic cancer vaccines like sipuleucel-T act as if you are pushing on the accelerator of your car. We also have immunotherapies that disable the "parking brake"! Ipilimumab (Yervoy), the first of this class of cancer immunotherapy, was approved by the FDA for the treatment of metastatic melanoma in 2011.

The development of ipilimumab resulted directly from a series of milestone discoveries by scientists in the field of immunology. What is most exciting about ipilimumab, is that some patients who

responded are still alive three, four, five years after receiving their treatment. This is something that has rarely happened before for patients with metastatic melanoma, and it indicates that even after their treatment was stopped, these patients' immune systems are still keeping their tumors in check.

In 2012 and 2013, the results of early-stage clinical trials testing immunotherapies that disable a second immune-system brake, called PD1, showed even more dramatic results. These studies reported frequent clinical responses not only for patients with metastatic melanoma, but also for those with kidney or lung cancer. Although these PD1-targeted treatments are not approved by the FDA currently, patients' responses seem to be long-lived, and everyone involved in the development of these drugs expects that they will soon become widely available.

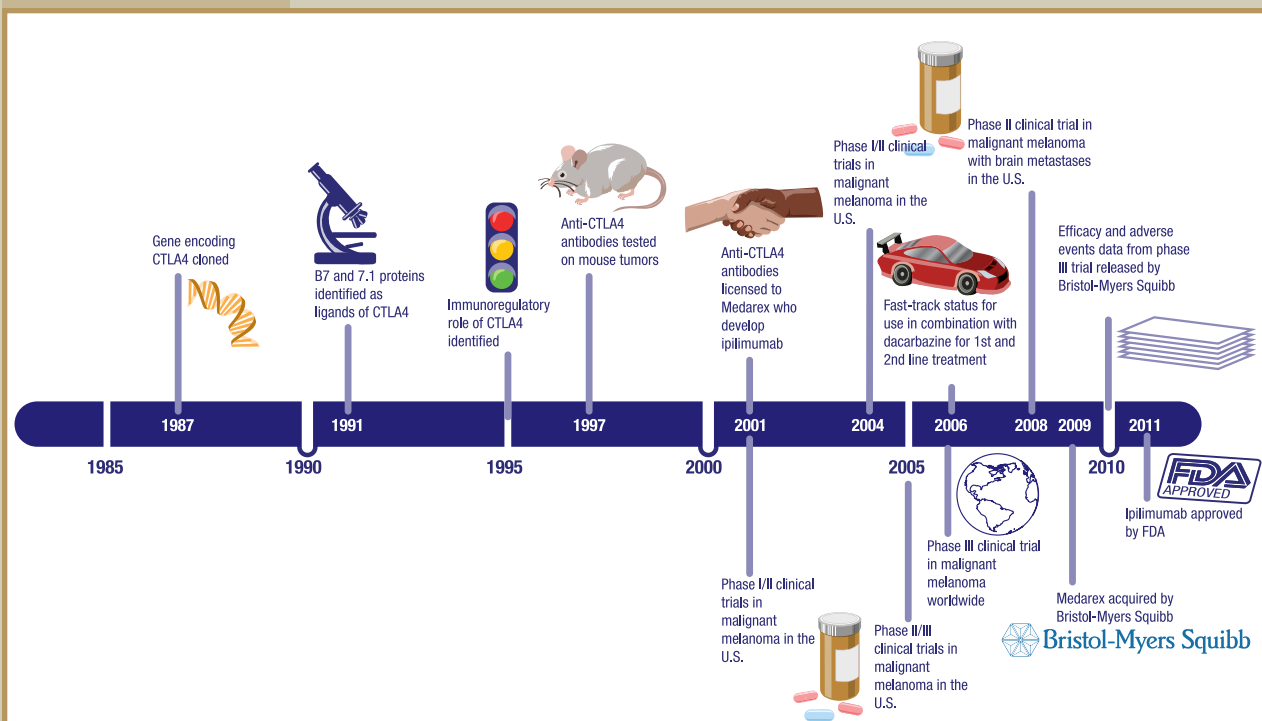
In the past, insufficient scientific understanding of the immune system has been a barrier to advancing immunotherapy as a treatment for cancer. Now that we have expanded our knowledge, we are no longer shooting in the dark; we are using science to guide the development of new approaches. Particularly exciting is the idea of combining immunotherapies that work in different ways. We have already seen this in the clinic, where a small clinical trial has confirmed the scientific prediction that a combination of ipilimumab and a PD1-targeted immunotherapy would be better than either treatment alone.

There is also a lot of reason to believe that some molecularly targeted therapies combined with epigenetic therapies will have huge effects on how the immune system interacts with a tumor. This opens the door to the possibility that combining these treatments with immunotherapies will provide additional clinical benefit.

When I was an oncology fellow, I was taught that there were three pillars of cancer treatment: surgery, radiotherapy, and chemotherapy. In the late 1990s, we added a fourth pillar, therapies that target specific cancer-driving defects. I have such confidence in the potential of immunotherapy that I think the years from 2010 to 2015 will be looked at historically as the time that immunotherapy became the fifth pillar of cancer treatment.

There are barriers to this becoming a reality, but they are not scientific. They are regulatory and financial. To use a military analogy, we have the weapons but not the funds to test or manufacture them quickly enough.

# Special Feature on Immunotherapy



**Figure 13: Stepping Toward the First Checkpoint Blockade.** Ipilimumab (Yervoy) is an immunotherapy that works by counteracting brakes on the immune system called immune checkpoint proteins. It was the first drug of its kind to be approved by the U.S. Food and Drug Administration (FDA). Almost 25 years of basic, translational, and clinical research underpinned the development of ipilimumab. The story began in 1987, when researchers discovered a gene that 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. There are now several other drugs in development against another checkpoint protein called PD1 (see **Table 9**, p 41).

## Therapeutic Antibody

A protein that attaches to a defined molecule on the surface of a cell. These agents can exert anticancer effects in several different ways.

surface high levels of molecules that act like brakes, making the T cells slow down and stop acting aggressively. This finding led researchers to seek ways to counteract these molecules, which are called immune checkpoint proteins.

The story of immune checkpoint proteins began in 1987, when researchers discovered a gene that they called CTLA4 (105) (see **Figure 13**). However, it took nearly eight years before the immune checkpoint function of CTLA4 was uncovered, and another 16 years of basic and clinical research before this knowledge was translated into a clinically effective therapy: a therapeutic antibody that targets CTLA4, ipilimumab (Yervoy). Upon attaching to CTLA4 on the surface of patients' T cells, ipilimumab releases the T cells' brakes, spurring them into action. This significantly prolongs survival for patients with metastatic melanoma (106). Ipilimumab was the first treatment in history to improve survival for patients with metastatic melanoma, and the FDA approved it for this use in March 2011.

## FDA Designations

To ensure the safety and efficacy of every drug in America, Congress established the U.S. Food and Drug Administration (FDA) in 1906. The FDA approves drugs after a rigorous evaluation process that can take many years to complete. In an effort to accelerate the pace at which new drugs reach patients with serious and life-threatening conditions like cancer, the FDA has introduced several new regulatory and review strategies.

### Breakthrough Therapy

Since 2012, experimental therapies that show substantial improvement over available treatments in early clinical studies are eligible for the breakthrough therapy designation. A drug that receives this designation is eligible for all of the features of fast track designation (see below) and additional guidance from the FDA throughout the drug development process. As of July 31, 2013, six anticancer drugs had received this designation, including two immunotherapies: Lambrolizumab for the treatment of advanced melanoma and obinutuzumab for the treatment of chronic lymphocytic leukemia.

### Fast Track

Fast track is designed to facilitate the development of drugs that fill an unmet medical need. This designation 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 that allows sponsors to submit to the FDA parts of the application as they are completed, rather than waiting until every section is finished. Ipilimumab (Yervoy), a treatment for metastatic melanoma, was approved through fast track in March 2011.

### Accelerated Approval

It can take many years to learn whether a drug improves or extends the lives of patients. To speed the evaluation process, the FDA will, in some cases, grant accelerated approval based on whether or not a drug affects a surrogate endpoint. Surrogate endpoints are scientifically validated measures likely to predict the treatment will have the intended clinical benefit (e.g., extending survival) and may include physical signs such as tumor shrinkage. Drugs approved based on surrogate endpoints must undergo additional testing to verify that they provide clinical benefit. Ponatinib (Iclusig), a treatment for chronic myeloid leukemia (CML), was approved under this pathway in December 2012.

### Priority Review

Drugs that have the potential to significantly improve safety or effectiveness may be granted priority review, which allows them to be assessed within six months as opposed to the standard ten months. The designation is granted after all clinical trials are completed, when the drug’s safety and efficacy can be reliably evaluated. Radium-223 dichloride (Xofigo) was granted priority review and approved for the treatment of prostate cancer that has spread to the bones in May 2013.

**Table 9: PD-1- or PD-L1-targeted Therapeutics Under Development**

Agent	Target
Lambrolizumab	PD-1
Nivolumab	PD-1
MPDL3280A	PD-L1
MEDI4736	PD-L2
AMP224*	PD-1

\*antibody-like protein

In some patients, ipilimumab’s effects on the immune system generate durable responses. In fact, about one in every five patients treated with only four doses of ipilimumab are still gaining benefit from it more than four years after completing therapy (105, 107). Ongoing clinical studies are investigating whether additional doses of ipilimumab can offer further benefit to patients like **Andrew Messinger**. Encouraging early results suggest that ipilimumab might also be effective against advanced lung cancer (108) and advanced prostate cancer (109), but these need verification in larger clinical trials.

The amazing success of ipilimumab has motivated researchers to develop similar therapies that target another immune checkpoint protein, called PD1, as well as therapies that target the protein to which PD1 attaches, PDL1 (see **Table 9**). Early clinical results with these therapies are very promising (110, 111), and large-scale clinical trials are currently ongoing.

One PD1-targeted therapy, nivolumab, has produced several responses persisting more than two years in a number of non-small cell lung cancer patients, advanced melanoma patients, and renal cell carcinoma patients (110, 112, 113). As a result of these encouraging data, the FDA granted nivolumab fast track designation for these cancers (see sidebar on **FDA Designations**).

### Change in Death Rates for MELANOMA (SKIN) (1990-2009)



EST. 2013 INCIDENCE = 76,690 • DEATHS = 9,480



## Andrew (Andy) Messinger

Age 61  
Short Hills, N.J.

### Beating Advanced Melanoma Since 2005

When I was diagnosed with melanoma eight years ago, I was shocked: I had never been a sun worshipper. In 2007, scans showed that the cancer had spread to my lungs, and in 2009, it spread to my brain. As a result of the brain lesion, I became eligible to participate in a clinical trial testing ipilimumab (Yervoy). I have been receiving ipilimumab through the clinical trial ever since and I am thankful every day that it has worked for so long.

It was 2005 when I first noticed a mark on my chest and went to see my dermatologist. He thought it was a blood blister so we were both very surprised when the biopsy revealed that it was melanoma.

My dermatologist referred me to Memorial Sloan-Kettering Cancer Center in New York, where I had the lesion surgically removed. I also had a sentinel lymph node biopsy. Unfortunately, this showed the cancer had spread to my lymph nodes and I had to have a second surgery to have lymph nodes removed. Although scans showed no sign of metastases in my body, the fact that the cancer was in my lymph nodes meant that my diagnosis was advanced disease.

At that point, there were limited treatment options available to me. It was do nothing and observe or treat with interferon. Although the use of interferon was very controversial, after speaking with multiple doctors to get their opinions, I decided that it was right for me. Psychologically, I just felt I needed to be treated.

Fortunately, I was able to get the initial interferon treatments locally, in suburban New Jersey. That helped a lot. After that, I continued with self-injection of interferon every other day for a year. During that time, I recuperated from my surgeries and resumed my life.

About a year after stopping interferon, scans showed tumors in my lungs. During the surgery to remove the affected parts of my lungs, the surgeon also removed several lymph nodes that were obviously cancerous. In an effort to slow the disease, I was treated with granulocyte-macrophage colony stimulating factor, or GM-CSF. It helped me for a few months, but then scans revealed more tumors in my lungs.

At that point, early 2008, I was not eligible for clinical trials testing a new therapy called ipilimumab that was being talked about on all the patient information blogs. So, I began four rounds of interleukin-2, or IL-2. The tumors shrank measurably. However, IL-2 was tough on my body, and then, in 2009, scans showed new tumors in my lungs and a lesion in my brain.

The brain lesion was a turning point, and if anyone can ever say they are lucky to have cancer in their brain, then I was very fortunate. I became eligible for a two-year clinical trial to study the effectiveness of ipilimumab on brain metastasis. I immediately enrolled. I experienced side effects and actually missed a round of treatment as a consequence, but my lung metastases disappeared. Ipilimumab was ineffective against my brain lesion, but this was successfully treated with radio-surgery. I also had radiation therapy to eliminate some lingering cancer in my humerus.

At the end of the two years, I had expected to stop ipilimumab treatment. After all, I had been receiving ipilimumab for two years, and the standard treatment for melanoma patients is four doses over the course of a year. However, the trial was extended for a number of individuals, including me, who had responded well to treatment. Because the goal is to determine whether continuing ipilimumab treatment provides benefit, I still receive ipilimumab quarterly.

Because I am benefiting so much from a clinical trial, I do everything I can to help move clinical research forward. In fact, I participated in clinical trials testing new advances in radio-surgery and radiotherapy during the course of my treatment.

I wish I had not had this experience, but I have, and I want people to understand that cancer is manageable, even deadly cancers like mine, and that there are reasons to be optimistic, even in the face of tough prognoses. The speed of progress in cancer research is such that the situation for patients can change very quickly. But to keep up the momentum, government needs to step up and fund cancer research in a much bigger way.

# Special Feature on Immunotherapy

The FDA has also designated lambrolizumab, a second therapeutic antibody that targets PD1, as a breakthrough therapy for advanced melanoma, after it was reported to benefit patients (114).

Despite the dramatic responses seen in some patients treated with ipilimumab, or an agent targeting PD1 or PDL1, these individuals are a small fraction of the total number of people affected by cancer. Perhaps the greatest promise of immunotherapy lies in combining immunotherapies that target different immune checkpoint proteins or immunotherapies that operate differently, as well as combining immunotherapies with other types of anticancer treatments.

To this end, a recent study suggests that combining ipilimumab and nivolumab shows promise, and a large-scale trial has been initiated to verify this hypothesis (115). In addition, an early-stage trial found that combining ipilimumab with sargramostim (Leukine), a synthetic version of an immune-system boosting substance naturally produced in the body significantly increased overall survival for patients with advanced melanoma (116). Thus, the potential of combining an immunotherapy that releases the brakes on the immune system with an immunotherapy that boosts the immune system is immense.

## Boosting the Killing Power of the Immune System

To return to the analogy of driving a car, another approach to immunotherapy is to step on the accelerator, enhancing the ability of the immune system to eliminate cancer cells. This can be done in several ways, including giving a patient a therapeutic vaccine or a form of treatment called adoptive immunotherapy.

A therapeutic vaccine trains a patient's immune system to recognize and destroy their cancer. The only therapeutic cancer vaccine currently approved by the FDA is sipuleucel-T (Provenge). It is a cell-based vaccine that was approved in 2010 for the treatment of advanced prostate cancer (117). Each patient receives a customized treatment that uses immune cells called dendritic cells from their own body to boost their cancer-fighting T cells. Researchers are currently conducting small clinical trials to examine whether the effectiveness of sipuleucel-T can be enhanced by combining it with the antihormone therapy abiraterone (Zytiga) (118).

The development of therapeutic cancer vaccines is an intensively studied area of cancer research. In the United States alone, there are several hundred ongoing clinical trials testing therapeutic cancer vaccines. Some are similar to sipuleucel-T, utilizing the patient's own dendritic cells, and these include one that has shown early promise as a treatment for colorectal cancer (119). Others operate in different ways, including one called PROSTVAC, which is being tested in a large clinical trial after early results indicated that it significantly increased survival for men with advanced prostate cancer (120).

Another therapeutic cancer vaccine clinical trial that has recently reported very encouraging early results is assessing the effectiveness of a combination of two vaccines, GVAX Pancreas and CRS-207, as a treatment for advanced pancreatic cancer (121). The two vaccines work together to boost patients' immune systems in different ways. GVAX Pancreas comprises pancreatic cancer cells that release GM-CSF, which generally enhances immune system function. CRS-207 is a nontoxic bacterial vaccine engineered to carry a protein that will boost the killing power of patients' immune cells. Experiments in mice originally showed that the combination of GVAX Pancreas and CRS-207 heightens the activity of a

## Pancreatic Cancer

kills more than 90 percent of patients within five years of diagnosis (1).



## Maddison (Maddie) Major

Age 8

La Plata, Md.

### Battling Acute Lymphoblastic Leukemia for More Than Half her Life

A message from **Robyn Major**,  
Maddie's mother

My daughter Maddie was diagnosed with acute lymphoblastic leukemia (ALL) when she was just three years old. She has been treated with all kinds of caustic chemotherapies and head-to-toe radiation therapy. But in January 2013, she received a therapy unlike any other she has been treated with: a T-cell therapy that is helping her own body fight the leukemia without serious side effects.

It all started in 2008. As we watched the July 4th fireworks in the summer heat, Maddie complained of being cold and tired. On top of this, a small bruise on her hip got bigger by the day until it looked like she had been beaten with a broom handle. Maddie's pediatrician suggested we take her straight to the emergency room at Children's National Medical Center in Washington, D.C., and blood tests there showed she had leukemia.

A bone marrow biopsy narrowed down the type of leukemia to B-ALL. She began the standard treatment for children with B-ALL, which is six months of intensive chemotherapy followed by two years of maintenance chemotherapy.

Unfortunately, Maddie's body did not respond well to the intensive chemotherapy. She spent two months in the intensive care unit on a ventilator and battling two life-threatening conditions: tumor-lysis syndrome, which caused liver failure; and sepsis, which was caused by an infection in the blood stream. When she finally came home, she had to relearn how to walk and talk.

Maddie, then 5, received her last dose of maintenance chemotherapy in October 2010, but life without treatment did not last long. We found out in February 2011, that she had relapsed.

Within days, Maddie started relapse therapy. This involved six months of even more intense chemotherapy than she had received previously, whole-body radiation therapy, cranial radiation, and a bone marrow transplant.

In August 2012, at just seven years old, Maddie relapsed for a second time. Further chemotherapy had no effect on Maddie's disease, and by December 2012, the doctors at Children's National

Medical Center told us that there was not much more they could do. We were devastated.

But a few days later, Maddie's oncologist called and said that she might be able to get Maddie enrolled in a clinical trial at Children's Hospital of Philadelphia. My first response was: You mean that was real? Several people had sent me links to stories on the internet about an experimental treatment at Children's Hospital of Philadelphia that had transformed the life of another girl with leukemia. I hadn't even read past the headlines thinking it was too good to be true.

It wasn't until after just Christmas that we went to see Dr. Grupp at Children's Hospital of Philadelphia. The wait had been excruciating and we had been afraid that it would be our last Christmas with Maddie. But the news he gave us — that the T-cell therapy might possibly be curative — blew us away. I remember thinking, if only we had known this 10 days ago, our Christmas would have been much happier.

In January 2013, we went back to Philadelphia so the doctors could collect Maddie's T cells. Then we faced another excruciating wait, which was about three weeks, as the T cells were genetically altered and grown in the lab. On Jan. 22nd, she got her T cells back. With the exception of a fever, headache, and some confusion, all of which resolved in a few days, she has experienced no side effects. It was such a different experience to all her other treatments.

Since then, the researchers have found no sign of leukemia in her blood or bone marrow and she is living the life she should. She swims, takes horseback riding lessons, and will start second grade on Aug. 19th; it will be the first time she has been in school since February 2012, when she was in kindergarten.

Maddie's experience has made me an advocate for research into pediatric cancers. The drugs that are used to treat many of these cancers are so toxic that they leave the children with a lifetime of problems: they stunt growth and lead to learning disabilities, heart problems, kidney problems, liver problems. These children are our future. We need a better way, and research holds the answers.

# Special Feature on Immunotherapy

group of cancer-fighting T cells. The fact that this combination almost doubled overall survival compared with GVAX Pancreas alone in a clinical trial (121), highlights the promise of combining immunotherapies that operate in different ways.

Adoptive immunotherapies are complex medical procedures that are built upon our accumulating knowledge of the biology of the immune system, in particular, T cells. There are no FDA-approved adoptive immunotherapies, but numerous approaches are currently being evaluated for several types of cancer.

Here, we highlight one adoptive immunotherapy that is showing considerable promise in adults with chronic lymphocytic leukemia and in some adults and children with acute lymphoblastic leukemia (122-125). A number of patients, including **Maddie Major**, have been in complete remission for many months, after their cancers failed to respond to other treatment options or relapsed after initially responding.

In this form of adoptive immunotherapy, T cells are harvested from the patient and genetically modified in the laboratory so that they attach to the surface of leukemia cells and are triggered to attack when they do. The number of genetically modified T cells, sometimes called CAR T cells, is expanded in the laboratory before they are returned to the patient, where they eliminate the leukemia cells.

As basic research continues to increase our understanding of how T cells function and how these functions can be exploited, new adoptive immunotherapies are likely to emerge in the near future.

## Flagging Cancer Cells for the Immune System

In order for the immune system to eliminate a cancer cell, it must find it first. Several of the therapeutic antibodies that have been approved by the FDA for the treatment of certain cancers (see **Appendix Table 1**, p. 81), and many of those in clinical trials, do just that. They operate, at least in part, by attaching to cancer cells expressing their target, flagging them for destruction by immune cells. Research into new and better targets for antibodies, as well as work on modifying the antibodies to help the immune system find them more easily, are creating exciting new experimental immunotherapies.

## Change in Death Rates for NON-HODGKIN LYMPHOMA (1990-2009)

18.6%



22.2%



EST. 2013 INCIDENCE = 69,740 • DEATHS = 19,020

The first therapeutic antibody the FDA approved for the treatment of cancer, rituximab (Rituxan), works in part by directing the immune system to cancer cells. Since its approval for certain forms of non-Hodgkin lymphoma in 1997, the FDA has also approved rituximab for the treatment of chronic lymphocytic leukemia. Perhaps more importantly, although an anticancer therapeutic, rituximab has also been approved by the FDA for the treatment of several autoimmune disorders — rheumatoid arthritis, granulomatosis with polyangiitis (also known as Wegener’s granulomatosis), and microscopic polyangiitis. Thus, rituximab is one of many examples of how investments made in cancer research have been magnified many times over for the benefit of the broader medical community (see sidebar on **Cancer Research at Work Against Other Diseases**, p. 46).

When used to treat cancer, rituximab functions by attaching to cancer cells that have the protein CD20 on their surface. Upon attaching to CD20, rituximab does several things that lead to the destruction of the cancer cells (126). One of these is that it attracts immune cells, including NK cells (see sidebar on **Key Players in the Immune System**, p. 38), which then destroy the cancer cells. A second is that it triggers within the cancer cells a series of events that cause the cells to die.

Even though rituximab has significantly increased survival for some cancer patients, a substantial number have disease that fails to respond to the initial treatment or eventually becomes resistant to it (126). Thus, many researchers have been working to develop more effective CD20-targeted therapeutic antibodies. Basic immunology research provided much insight, including a detailed molecular understanding of how rituximab attracts immune cells and instructs them to destroy the cancer cells (127). This knowledge led bioengineers to create the next



# Special Feature on Immunotherapy

## Cancer Research at Work Against Other Diseases

The initial investments in developing anticancer agents are greatly magnified when a given agent is approved for additional uses against both cancer and other diseases. Below are some examples of anticancer agents that are benefiting patients with other diseases.

Bevacizumab (Avastin) was first developed and approved for the treatment of metastatic colorectal cancer in 2004, and was subsequently approved for the treatment of kidney cancer. The clinical success of bevacizumab enabled the development of two related therapies ranibizumab (Lucentis) and aflibercept (Eylea) for the treatment of wet macular degeneration, a disease of the eye that ultimately leads to blindness. The elderly and patients with type 2 diabetes mellitus are at increased risk for wet macular degeneration. Thus, these drugs will effectively prevent a growing number of people from going blind, thanks to cancer research.

Methotrexate was first developed and used to treat hematologic malignancies such as acute lymphoblastic leukemia in the early 1950s, and was subsequently approved for the treatment of at least six additional types of cancer. It also is a very effective treatment for patients with psoriasis and severe rheumatoid arthritis.

Paclitaxel was first developed and approved for the treatment of ovarian cancer in 1992, and was subsequently approved for the treatment of several other cancers. Now, many patients with blocked arteries benefit from several different paclitaxel-coated stents. Stents are stiff meshes that physically keep arteries open after a blockage has been cleared. However, cells in the artery walls often grow through the mesh and reblock the artery. Paclitaxel is extremely effective at preventing this reblockage of the artery. Thus, many cardiovascular patients have benefited from cancer research.

Recombinant alpha interferons were first approved for the treatment of hairy cell leukemia in 1986, and were subsequently approved for the treatment of several other cancers. Now, they are used to treat adults suffering from chronic hepatitis B and/or C virus infections and children with chronic hepatitis B virus infection, as well as those with HPV-associated genital warts, dramatically increasing the number of individuals benefiting from cancer research.

Rituximab (Rituxan) was originally developed to treat non-Hodgkin lymphoma and chronic lymphocytic leukemia, but has subsequently been approved by the FDA for the treatment of several autoimmune disorders — rheumatoid arthritis, granulomatosis with polyangiitis (also known as Wegener's granulomatosis), and microscopic polyangiitis.

## Change in Death Rates for HODGKIN LYMPHOMA (1990-2009)

43.5%



36.0%



EST. 2013 INCIDENCE = 9,290 • DEATHS = 1,180

generation of CD20-targeted antibodies with enhanced ability to recruit immune cells and direct them to attack the cancer cells (126).

Obinutuzumab is the most promising of the new CD20-targeted antibodies. Compared with rituximab, obinutuzumab is better at recruiting and instructing immune cells to kill cancer cells and better at directly killing the cancer cells themselves (128). Early-stage clinical trials have indicated that obinutuzumab may provide an effective new treatment option for patients with non-Hodgkin lymphoma or chronic lymphocytic leukemia that has failed to respond to prior therapies or has relapsed after initially responding to earlier treatments (129, 130).

The results of these studies were so promising that the FDA granted obinutuzumab breakthrough therapy designation (see sidebar on **FDA Designations**, p. 41). Larger trials are underway, with initial results indicating that obinutuzumab significantly delays disease progression for patients with previously untreated chronic lymphocytic leukemia and suggesting that it might be more effective than rituximab (131). The final results of these trials are eagerly awaited.

The immunotherapies highlighted in this **Special Feature on Immunotherapy** (p. 38) underscore how decades of research in numerous disciplines are paying dividends for many cancer survivors, like **Andrew Messinger** and **Maddie Major**. Pursued for years by many researchers across the biomedical research enterprise, the dream of immunotherapy is 110 years old. However, we are now much closer to realizing the dream as immunotherapies are delivering robust and lasting responses for some patients with several different forms of cancer.

## Molecularly Targeted Therapies

Research is continually expanding our understanding of cancer biology, making it increasingly possible to link specific defects in the molecular machinery of cells to cancer development. This knowledge is directly enabling the development of medicines that precisely target these alterations and block their ill effects. As a result, the standard of care is transforming from a one-size-fits-all approach to one in which the molecular makeup of the patient and of the tumor dictate the best therapeutic strategy. This approach is variously called personalized cancer medicine, molecularly based medicine, precision medicine, or tailored therapy.

The number of molecularly targeted therapies approved by the FDA is increasing, and is expected to continue to grow as our knowledge of cancer biology expands. Because of the greater precision of many of the newest cancer medicines, they are more effective and 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 are also improving their quality of life.

### A Direct Hit: Targeting Chemotherapy to Breast Cancer

It is anticipated that in 2013, more than 45,000 individuals in the United States will be diagnosed with breast cancer that overexpresses the protein HER2 (1, 132). HER2-positive breast cancer tends to be aggressive, and the outcome for patients is typically poor. Decades of research led to the development and FDA approval of three HER2-targeted therapies that have revolutionized the treatment of this disease: trastuzumab (Herceptin), lapatinib (Tykerb), and pertuzumab (Perjeta) (see **Table 10**). These drugs significantly prolong survival for patients with metastatic disease when given together with standard chemotherapies (133-135). Unfortunately, some patients fail to respond to treatment, and in most of those who do respond initially, the disease ultimately progresses. As a result, new therapies for this subtype of breast cancer are urgently needed and are being actively researched.

An exciting new treatment for patients with metastatic HER2-positive breast cancer, like **Kim Alexander**, was approved by the FDA in February 2013. The drug, ado-trastuzumab emtansine (Kadcyla), which was referred to as T-DM1 during clinical development, is an antibody-drug conjugate. Antibody-drug conjugates are a new type of targeted anticancer therapy, which use an antibody to deliver an attached drug directly to those cancer cells that display the antibody's target on their surfaces. This precision reduces the side effects of the drugs compared with traditional chemotherapy that is delivered systemically. In the case of T-DM1, the chemotherapy DM1 is attached to the antibody trastuzumab using a stable linker. The HER2-targeting properties of trastuzumab allow T-DM1 to be delivered directly to HER2-positive cells. The result is a significant improvement in survival for many patients (132).

The development of antibody-drug conjugates is an intensively studied area of cancer research that is showing great promise for near-term patient benefit. In the United States alone, approximately 80 clinical trials are either ongoing or actively recruiting patients to test antibody-drug conjugates as a treatment for

**Table 10: Currently Approved Human Epidermal Growth Factor 2 (HER2) Targeted Drugs**

Generic Name	Trade Name	Formulation
ado-trastuzumab emtansine	Kadcyla	
lapatinib	Tykerb	
pertuzumab	Perjeta	
trastuzumab	Herceptin	

## Invasive Breast Cancer

An estimated 2240 men and 232,340 women will be diagnosed with **invasive breast cancer** in 2013, and an estimated 410 men and 39,620 women will die from their disease (1).

### Change in Death Rates for BREAST CANCER (1990-2009)

**32.9%**



EST. 2013 INCIDENCE = 234,580 • DEATHS = 40,030

## Kim Alexander

Age 55  
Gallatin, Tenn.

### Living with Inflammatory Breast Cancer Since 2006.



I was diagnosed with HER2-positive, stage III inflammatory breast cancer in October 2006. It progressed to metastatic cancer in May 2009. By December 2010, I had undergone several different treatments and participated in several clinical trials, but my cancer was no longer responding and the treatments were very toxic to my body. I was ready to give up. I agreed to enroll on one last clinical trial. It was testing a drug called T-DM1 (Kadcyla). It handed me my life back, and then some — I'm happier than I have ever been.

It all started in September 2006. I was riding a horse that I had recently purchased, and I suddenly felt severe pain in my breast. When I looked, I discovered my breast was extremely enlarged. Despite this, it was another three weeks before I went to a gynecologist because I had heard about something called inflammatory breast cancer, and I needed to wrap my mind around the awful possibility that I might have something that serious.

The gynecologist sent me straight to a breast specialist, who confirmed my fears immediately. Being told that you have inflammatory breast cancer and that it is the worst type of breast cancer was terrifying. I was immediately thrown into a world that I knew nothing about — treatments, surgeries, breast cancer markers. I had to become an expert really quickly.

My initial treatment was chemotherapy. Because my tumor was HER2-positive, I first received two chemotherapy drugs and then trastuzumab (Herceptin), which targets HER2, and paclitaxel (Taxol). After a short break, I had surgery, which was followed by a year of treatment with trastuzumab.

Just six months after stopping treatment with trastuzumab, I found out that my cancer had progressed. For the next 18 months I received various existing treatments and participated in a number of clinical trials. Some of the drugs or drug combinations benefited me for a time, but none had a lasting effect.

After the fourth or fifth treatment, I was so sick that I decided to tell my doctor that I wanted to stop treatment. However, she talked me in to enrolling in a phase III clinical trial at Sarah Cannon in Nashville, Tenn., which was testing T-DM1. Enrolling in the trial changed my life.

I received my first dose of T-DM1 in December 2010. Initially, T-DM1 controlled my cancer, then it started to shrink it, and by December 2011, there was no sign of it. It was an amazing moment, and one that I had not expected.

My decision to enroll on the T-DM1 clinical trial turned my life around almost immediately. I had been ready to throw my life away, but the dynamic, upbeat attitude at Sarah Cannon, where there was no consideration that I was a dying person, coupled with the fact that my cancer was responding to T-DM1, enabled me to start thinking about my future. I felt so positive that just a month after enrolling in the trial, I adopted an unwanted, neglected thoroughbred ex-racehorse and made plans for his future as a dressage horse.

I still receive T-DM1 every three weeks, and my scans continue to show no sign of disease. I'm extremely healthy, I'm spending most of my time outdoors, and I'm living a life that is, in many ways, higher quality than it was before my diagnosis.

There are two things that I have learned from my experience with cancer. First, cancer is not a death sentence and you must not stop living. If your doctor makes you feel that there is no hope, then you need to consider finding a new one. Second, clinical research saves lives. It saved my life and has saved the lives of many of my friends. Without it, cancer will beat us all.

several cancers. Leveraging our current knowledge of conventional chemotherapies and of the precision targeting of anticancer antibodies to develop new antibody-drug conjugates not only improves patient care by reducing side effects, but it also increases the return on prior investments in cancer research.

### Blocking Tumor Sustenance

Research has shown that many solid tumors are very dependent on the growth of new blood and lymphatic vessels to grow and survive. Thus, targeting these key components of the tumor microenvironment provides an ideal avenue for therapy.

Since February 2004, the FDA has approved nine drugs that work in similar ways to impede the growth of the new blood and lymphatic vessel networks that enable cancer cells to thrive (see **Table 3**, p. 16). These drugs mainly function by stopping members of a family of growth-promoting proteins called VEGFs from activating the molecules they attach to, VEGF receptors, which are mostly found on blood and lymphatic vessel walls.

These therapies have had the biggest impact for patients with the most common type of kidney cancer in adults, renal cell carcinoma. However, they also greatly benefit those with the most aggressive form of liver cancer, as well as patients with some forms of pancreatic cancer; some gastrointestinal stromal tumors and soft-tissue sarcomas; and some colorectal, lung, and thyroid cancers.

One new therapeutic option in this growing class of drugs is cabozantinib (Cometriq), which was approved by the FDA for the treatment of metastatic thyroid cancer in November 2012 (136). In addition, in September 2012, the FDA approved regorafenib (Stivarga) for the treatment of metastatic colorectal cancer, after it was shown to significantly prolong patient survival (137). In light of the results of a large trial that showed that regorafenib increased by more than fourfold the time before disease progressed for patients with advanced gastrointestinal stromal tumors, the FDA approved regorafenib for the treatment of this disease in February 2013 (138).

The nine FDA-approved drugs that block VEGFs or the function of VEGF receptors are currently being tested in numerous clinical trials as treatments for several additional forms of cancer. One promising clinical trial is examining the utility of pazopanib (Votrient) as a treatment for patients with advanced ovarian cancer (139). Also encouraging are the initial results of a large trial testing sorafenib (Nexavar) as a treatment for certain patients with thyroid cancer (140). Determining if treatments for certain cancers might benefit other groups of patients not only improves patient care, but it also has the added bonus of increasing the return on prior investments in cancer research.

In February 2013, the FDA approved Pomalidomide (Pomalyst) for the treatment of multiple myeloma. Pomalidomide is a member of a family of drugs called immunomodulatory drugs. These drugs fight multiple myeloma by modulating aspects of the immune system and by reducing the production of VEGFs, which leads to disruption of new blood and lymphatic vessel networks (141). Importantly,

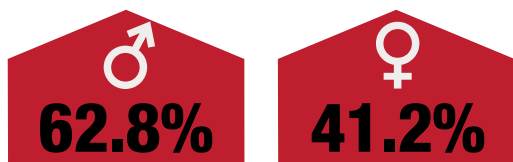
## Inflammatory Breast Cancer

is a rare and very aggressive type of breast cancer. It accounts for 1 to 5 percent of all breast cancers diagnosed in the United States.

## Ovarian Cancer

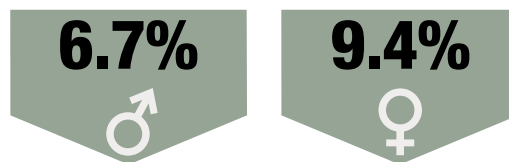
Patients with **ovarian cancer** that has metastasized to distant sites have a five-year survival rate of around 30 percent (1).

### Change in Death Rates for LIVER & BILE DUCT CANCER (1990-2009)



EST. 2013 INCIDENCE = 30,640 • DEATHS = 21,670

### Change in Death Rates for KIDNEY CANCER (1990-2009)



EST. 2013 INCIDENCE = 65,150 • DEATHS = 13,680

## Drug Resistance

Despite the major advances we have made in treating cancer, many tumors are not completely eliminated by the therapies that we currently use and, over time, become resistant to a given therapy and continue to progress.

Drug resistance is of two types: acquired resistance, which develops during the course of treatment in response to therapy, and innate resistance, which is inherent and present even before treatment with a given therapy begins. It is one of the greatest challenges that we face today in cancer treatment.

Diversity among the cancer cells in a single tumor is a key driver of acquired resistance to treatment with both cytotoxic and molecularly based therapeutics. For example, many cytotoxic drugs are designed to target only rapidly dividing cells, and so cells within a cancer that are not rapidly dividing escape these treatments. In addition, dividing cancer cells accumulate new genetic changes at a high rate. In cancers being treated with molecularly targeted therapies, if one cell gains a new mutation that alters the drug target itself, the drug may be ineffective against that cell, which will then continue dividing.

Redundancies among the signaling networks that fuel cancer cell proliferation can also permit cells to become resistant to molecularly targeted therapies. In this case, the initial therapeutic can block a signaling pathway in the network, but the cell uses a “detour” around the blockade and continues proliferating.

Some patients, despite having the molecular defect that matches a given molecularly targeted drug, do not respond to the therapy because of innate resistance. This may be because of genetic mutations present in the cell itself, or it could be because of a variation in the patient’s genome that alters drug activity or metabolism, or a combination of the two.

To develop therapies that will overcome drug resistance, we need to continue making inroads in understanding the ways by which cancers become drug resistant, as well as the factors within the tumor and the patient that drive resistance. This will only be possible with continued investment in the research to do so.

## Change in Death Rates for LEUKEMIA (1990-2009)

11.0%



15.0%



EST. 2013 INCIDENCE = 48,610 • DEATHS = 23,720

## Change in Death Rates for MYELOMA (1990-2009)

12.4%



16.6%



EST. 2013 INCIDENCE = 22,350 • DEATHS = 10,710

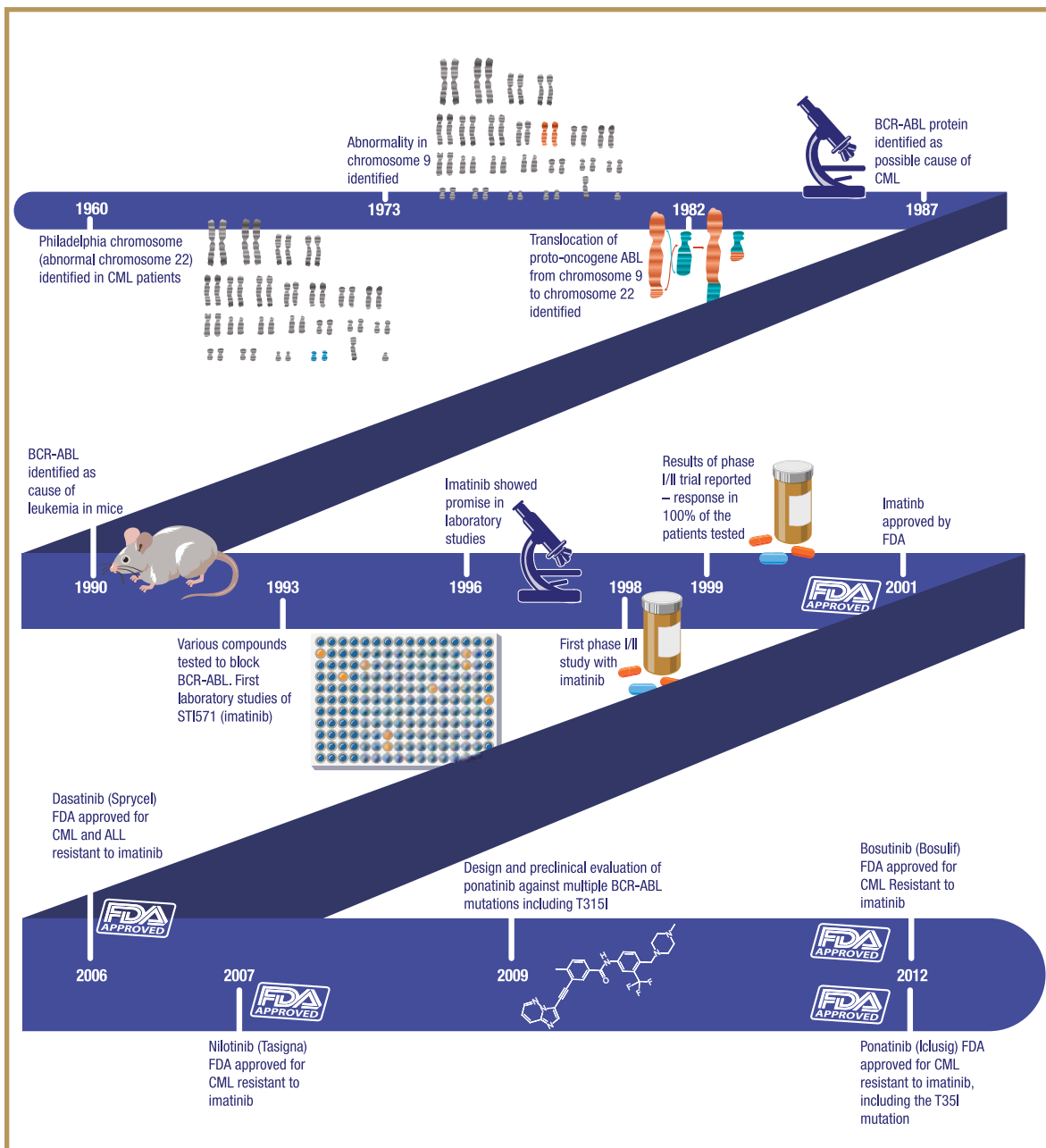
pomalidomide benefits patients with multiple myeloma that has progressed after treatment with earlier generation immunomodulatory drugs (142).

### Lessons Learned From CML

Imatinib (Gleevec) was the first molecularly targeted chemical approved by the FDA for the treatment of a cancer, CML. Its development was the result of a series of groundbreaking scientific discoveries (see **Figure 14**, p. 51). Imatinib blocks the activity of an aberrant protein called BCR-ABL, which fuels most cases of CML. Five-year survival rates for CML increased from just 31 percent to around 90 percent following the 2001 FDA approval of imatinib (1, 143). Unfortunately, a small fraction of patients never respond to imatinib, while other patients initially respond, but eventually their leukemia returns, or relapses, having acquired resistance to the drug (see sidebar on **Drug Resistance**).

Researchers have determined that imatinib-resistant leukemias harbor unique forms of BCR-ABL that cannot be blocked by the drug. Two second-generation drugs, dasatinib (Sprycel) and nilotinib (Tasigna), that are able to block most of these distinctive BCR-ABL proteins, were developed and approved by the FDA in 2006 and 2007, respectively. However, all three drugs fail to block one particular form of BCR-ABL, called T315I, which remains a significant challenge.

Three FDA decisions in the last four months of 2012 should help address this serious clinical issue and has increased the number of treatment options for patients with imatinib-resistant CML. The first was the September 2012 FDA approval of bosutinib (Bosulif). Like imatinib, dasatinib, and nilotinib, bosutinib blocks the activity of BCR-ABL but fails to block the T315I BCR-ABL mutant. Its use as a treatment for CML was approved by the FDA after it was shown to have anti-leukemic activity in patients with CML resistant to one or more of imatinib, dasatinib, and nilotinib (144). The second was the October 2012 FDA approval of omacetaxine mepesuccinate (Synribo). Understanding how omacetaxine mepesuccinate works is an area of active investigation; currently, it seems that



**Figure 14: The Pathway to Progress Against Chronic Myelogenous Leukemia.** The development of the first molecularly targeted therapy approved by the U.S. Food and Drug Administration (FDA), imatinib (Gleevec), was the culmination of numerous groundbreaking discoveries. The story began in 1960, when it was noted that the majority of patients with chronic myelogenous leukemia (CML) had an abnormal chromosome 22, which was called the Philadelphia chromosome. It was another 13 years before the abnormal chromosome 9 was discovered, and even longer before it was shown that translocation between the two chromosomes created the Philadelphia chromosome and generated an entirely new protein, BCR-ABL, the activity of which was likely the cause of CML. As a result, drugs that shut off BCR-ABL were developed, entering clinical trials in 1998 and being FDA-approved for the treatment of Philadelphia chromosome–positive CML in 2001. Subsequently, identification of imatinib-resistant patients led to the development and FDA approval of dasatinib (Sprycel) in 2006, nilotinib (Tasigna) in 2007, and bosutinib (Bosulif) in 2012. However, none of these drugs were effective against the T315I BCR-ABL mutation. In late 2012, the FDA approved ponatinib (Iclusig) for the treatment of T315I-mutant CML, and the drug is now benefiting many patients, including **Hans Loland**; see p. 52.



## Hans Loland

Age 45  
Woodinville, Wash.

### Living with Chronic Myelogenous Leukemia (CML) Since 2008

When I was diagnosed with chronic myelogenous leukemia (CML) in December 2008, my hopes and dreams were taken from me suddenly. I had a two-year old son and my wife was six months pregnant with our second child. I went from assuming I would see my children grow up, to wondering if I would see my first child start kindergarten. Thanks to a clinical trial that enabled me to receive the drug ponatinib (Iclusig), my dreams have come back. My wife and I have had a third child, and my oldest son started kindergarten last fall.

I am an avid soccer player. In the fall of 2008, I started feeling extremely tired during games and having to sub out a lot. I was also experiencing night sweats. My wife talked me into going to my doctor. He sent me for what I thought would be a routine blood test. However, the next day he called me back and told me to come into the office immediately. I don't remember much about that appointment after my doctor opened by telling me I had leukemia, I was in complete shock.

The blood test didn't tell my doctor what type of leukemia I had, so I was sent for a bone marrow biopsy. The results showed that I had CML. Standard treatment was imatinib (Gleevec), which I learned from my doctor put many patients in long-term remission. That gave me some hope.

After taking imatinib for just a few days, I started feeling much better. Thirty days later, my first blood test showed positive signs too. However, when my bone marrow was analyzed six months after I started imatinib, there were just as many leukemia cells as there had been at my diagnosis. This setback was devastating.

To understand why imatinib had not worked for me, my leukemia cells were analyzed for mutations, but this gave no clear answers. I was told my best option was to begin taking dasatinib (Sprycel). I sought a second opinion from Dr. Druker at the Knight Cancer Institute at Oregon Health & Science University, who agreed but cautioned me that there was a 50 percent chance that it would not work.

Unfortunately, Dr. Druker was right. After taking dasatinib for three months, analysis of my bone marrow showed my leukemia had not responded to treatment. A second mutation analysis provided the explanation: my leukemia cells carried the T315I mutation that made them resistant to imatinib, dasatinib, and all other targeted therapies approved for CML at the time.

A bone marrow transplant seemed to be my only option, and I began preparing for it. However, I wanted to avoid it if I possibly could. I couldn't fathom having to go through a physically extreme treatment that would involve my being unable to hug my children for 100 days.

I was lucky, I managed to find and enroll in a phase I clinical trial that was evaluating a drug, ponatinib, designed to treat T315I mutant CML. I received my first dose of ponatinib in November 2009. Six weeks later, right before Christmas, I got the best present ever: my test results showed that the drug was working. Finally I felt I could breathe.

More good news followed: at the three month mark my bone marrow showed no sign of leukemia cells, and for the past two years, my leukemia has been undetectable using the most sensitive test that exists. Although this does not mean I am cured, and I know that the cancer might reemerge, I am hopeful that my remission will be long term.

When I look back, I see how very fortunate I was to enroll in the trial. My best friend was diagnosed with CML just a few months before me and he was not so lucky. Although his leukemia went into remission after a bone marrow transplant, it later returned and he succumbed to the disease. But thanks to ponatinib, and to Dr. Deininger and Dr. Mauro, who throughout the trial made sure to treat me, not just the CML, I feel great, I am a hands-on dad to three healthy young boys, I have a full-time job, I play soccer, and I do everything I want to in life because CML doesn't hold me back.

it does not directly block BCR-ABL activity but rather reduces levels of BCR-ABL protein. Perhaps as a result of its unique mode of action, early clinical studies indicate that omacetaxine mepesuccinate has clinical benefit in patients with CML harboring the T315I BCR-ABL mutant (145).

The third decision is the December 2012 FDA approval of ponatinib (Iclusig), a drug that is transforming the lives of patients like **Hans Loland**, who has CML harboring the T315I BCR-ABL mutant. The development of ponatinib culminated in a clinical trial that showed that ponatinib benefited patients with CML resistant to multiple other BCR-ABL–blocking drugs (146). Most dramatically, it was effective for nearly all patients with CML harboring the T315I BCR-ABL mutant. Although it is too soon to tell how long ponatinib will control disease, early signs are very promising.

### Two Drugs: One Cancer-driving Pathway

In 2011, the FDA revolutionized the treatment of metastatic melanoma, the most aggressive form of skin cancer, when it approved vemurafenib (Zelboraf). This drug blocks an abnormal form of the signaling protein BRAF, called BRAF V600E, which fuels about 45 percent of melanomas (147). Thus, the FDA approved the use of vemurafenib only for patients who have metastatic melanoma shown to be driven by BRAF V600E as identified using a special test, a companion diagnostic, called the cobas 4800 BRAF V600 Mutation Test (see sidebar on **Companion Diagnostics**).

## Companion Diagnostics

The effective therapeutic use of most drugs targeting particular cancer-driving molecular abnormalities requires tests, called companion diagnostics, that can accurately match patients with the most appropriate therapy. Patients positively identified by a test can rapidly receive a treatment to which they are very likely to respond. Those patients identified as very unlikely to respond can be spared any adverse side effects of the therapy and immediately start an alternative treatment, saving them precious time in their race to find an effective therapy. Moreover, definitive stratification of patient populations can also provide substantial health care savings by avoiding the deployment of ineffective courses of cancer treatments and the costs associated with their adverse effects.

Without the ability to accurately match patients with the most appropriate therapies, some anticancer drugs would be clinically useless because the personal and financial costs would far outweigh the benefits. For example, the drug crizotinib (Xalkori), which dramatically improves the survival of patients with non-small cell lung carcinoma harboring ALK gene alterations, would be clinically useless without its companion diagnostic because only about 5 percent of non-small cell lung carcinomas are driven by ALK gene alterations.

Further advances against metastatic melanoma were made in May 2013, when the FDA approved two new drugs, dabrafenib (Tafinlar) and trametinib (Mekinist) (148, 149). Like vemurafenib, dabrafenib specifically blocks the activity of BRAF V600E, and the FDA approved its use only for patients with metastatic melanoma shown to be driven by BRAF V600E as identified by the cobas 4800 BRAF V600 Mutation Test or the newly FDA-approved THxID BRAF test.

In contrast to vemurafenib and dabrafenib, trametinib blocks the activity of two proteins called MEK1 and MEK2, which function in the same signaling network as BRAF V600E (see **Figure 15**, p. 54). As the MEK proteins come after BRAF V600E in the pathway, trametinib is effective against the estimated 5 percent of metastatic melanomas fueled by other abnormal BRAF proteins, most prominently BRAF V600K, which are detected by the THxID BRAF assay but not the cobas 4800 BRAF V600 Mutation Test (149).

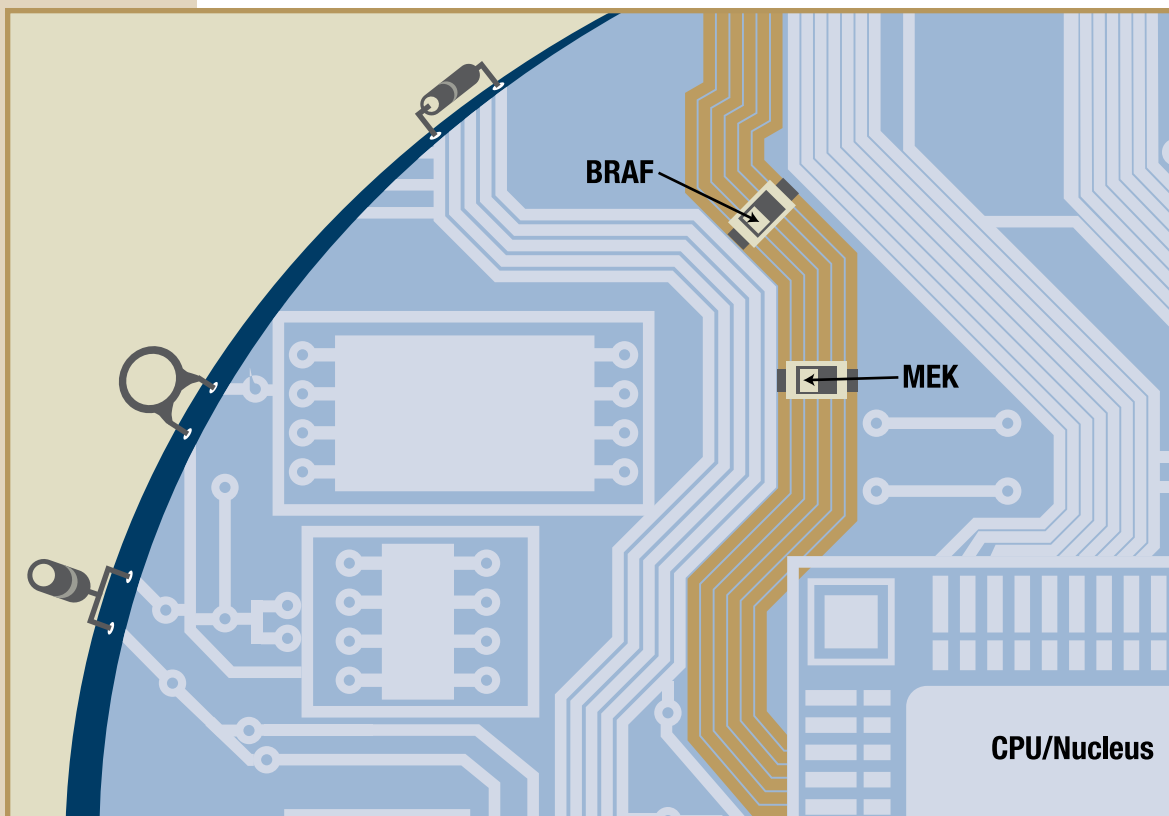
Despite the positive clinical responses achieved with vemurafenib, dabrafenib, and trametinib, most patients relapse within one year of starting treatment (147-149). Based on these data and other preclinical research, it was thought that because dabrafenib and trametinib block different components of the same cancer-driving signaling network, a combination of the two drugs may be more effective for metastatic melanoma patients compared with either drug alone. Early clinical trials suggest this hypothesis may be true because the combination of drugs is nearly doubling the length of time before the disease progresses (150). Based on promising clinical results, an application for the use of this combination of drugs for the treatment of metastatic melanoma was filed for FDA review in July 2013. This approach provides a window into the near-term future of molecularly targeted therapy: rational combination of treatments grounded in our understanding of cancer biology (see **On The Horizons**, p. 63).

### Helping Some Lung Cancer Patients Breathe Easier

Lung cancer is the leading cause of cancer-related deaths among men and women in the United States, with 159,480 Americans predicted to die from the disease in 2013 (1). Non-small cell lung carcinoma accounts for about 85 percent of lung cancer cases. About 10 percent of non-small cell lung carcinomas are a result of mutations in the EGFR gene. In order to help direct EGFR-targeted therapies to these patients, the FDA approved a companion diagnostic (the cobas EGFR Mutation Test) to detect the two most common EGFR mutations found in non-small cell lung carcinomas, in May 2013.

The development and approval of this companion diagnostic greatly facilitated the May 2013, FDA approval of the EGFR-targeted therapy erlotinib (Tarceva) as the first treatment for





**Figure 15: Signaling Networks: The Cell's Circuitry.** Just as a circuit board has many interacting circuits to perform its various functions, so too, do cells. Cellular circuits are referred to as signaling networks, each of which carries out a primary function, and also interacts with other parts of the network or other networks. Here, a few of the interacting cellular signaling networks are depicted as electronic circuits; the highlighted circuit is a simplified representation of the MAPK signaling network critical to many cancers. Although there are two points in the highlighted circuit at which it can be inactivated, there are multiple points at which the MAPK signaling network can potentially be inactivated. Mutations in the BRAF component of the MAPK signaling network (switch) that enhance network activity often drive melanoma. However, drugs that inactivate this point in the network (vemurafenib and dabrafenib) do not eliminate all BRAF-activated melanoma cells. By inactivating a second component of the MAPK signaling network, MEK (switch), with the drug trametinib, more of the melanoma cells can be eliminated.

## Lung Cancer

Just 16 percent of **lung cancer** patients survive five years after diagnosis (1).

patients with metastatic non-small cell lung carcinoma driven by either of the mutations detected by the diagnostic — EGFR exon 19 deletions or an EGFR exon 21 L858R substitution. Prior to the approval of the companion diagnostic, oncologists could only use erlotinib to treat patients with metastatic non-small cell lung carcinoma after they had received at least one other therapy. Thus, the companion diagnostic is helping a substantial number of patients with non-small cell lung carcinoma save time in their quest to find the best drug to treat their cancer.

In July 2013, the FDA approved a new EGFR-targeted therapy, afatinib (Gilotrif), for the treatment of patients with non-small cell lung carcinomas with EGFR exon 19 deletions or an EGFR exon 21 L858R substitution. Patients with these mutations can be identified using the cobas EGFR Mutation Test or the theascreen EGFR RQ PCR Kit, which was FDA approved at the same time as afatinib. The ability of these companion diagnostics to hone in on those patients most likely to benefit from afatinib (151) provides an example of the importance of developing new anticancer drugs alongside companion diagnostics to ensure that they reach the patients who need them as quickly as possible.

## Closing RANK on a Rare Bone Tumor

In June 2013, the FDA approved a new use for the therapeutic antibody denosumab (Xgeva). It can now be used to treat giant cell tumor of bone, an uncommon disease for which treatment options had barely changed in the past three decades. Giant cell tumor of bone rarely metastasizes and is most commonly treated with surgery (152). Although this cures some patients, it causes substantial morbidity, and in many cases tumors recur. Moreover, some patients have tumors that cannot be removed with surgery, and denosumab has been shown to provide substantial benefit in these cases (153).

Advances in our understanding of normal bone biology were central to the clinical development of denosumab, which targets the protein RANKL on the surface of certain bone cells. Normally, RANKL activates these cells causing a reduction in bone density and strength. Thus, blocking RANKL with denosumab strengthens bones. As such, it was first developed and FDA approved for the treatment of postmenopausal women with osteoporosis who were at high risk for fractured bones; it was subsequently approved by the FDA for the prevention of fractures caused by cancer metastases to the bone. Thus, the FDA approval of denosumab for giant cell tumor of bone not only benefits patients with this cancer, but it also increases the return on prior investments in cancer research.

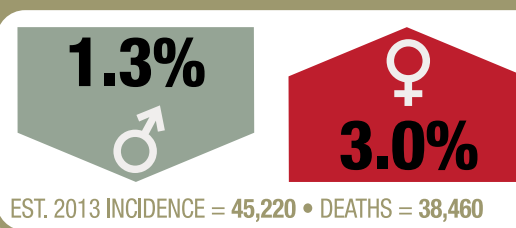
## Technology Advances for Patient Benefit

Technologies ranging from the earliest microscopes to our most advanced whole-genome sequencing machines have enabled us to achieve our current comprehensive understanding of the biology of cancer. They are also increasingly being exploited for the benefit of patients. Here, we discuss some of the recent technological advances that are being harnessed to detect, diagnose, and treat many forms of cancer. These advances are but a glimpse of what is to come; there are many innovative technologies under development that are poised to revolutionize cancer medicine in the near future.

### Nanotechnology: Tiny Technologies Make a Big Impact

Nanotechnology refers to the manufacturing of objects with dimensions one million times smaller than a millimeter (the smallest width of a human hair is just fifty times smaller than a millimeter). Nanomedicine is the application of nanotechnology to the research and practice of medicine. Nanodrugs comprise an anticancer agent and a nanosized carrier that is designed in such a way that it selectively delivers the drug to the cancer and protects the drug from being destroyed by the body's

## Change in Death Rates for PANCREATIC CANCER (1990-2009)



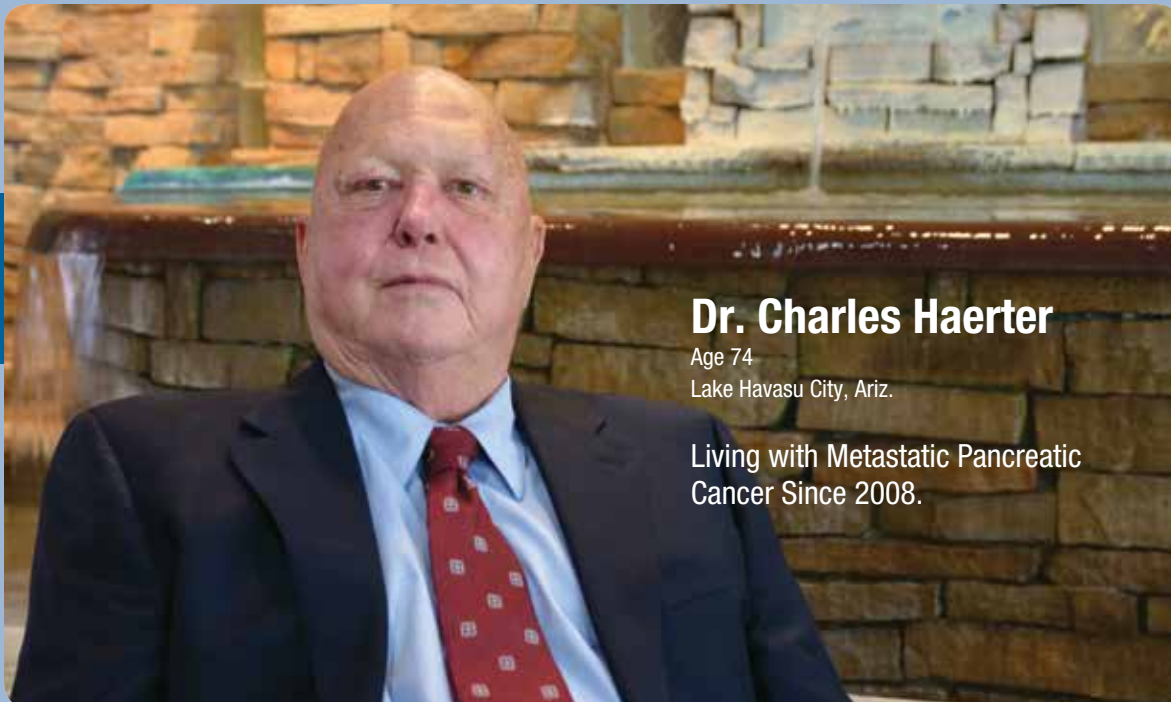
defenses during transport. As a result, nanodrugs allow the delivery of higher levels of anticancer agents to cancer cells than traditional systemic delivery methods, increasing effectiveness while reducing toxic side effects.

The conventional chemotherapy paclitaxel (Taxol) is used to treat some breast, ovarian, and lung cancers, specifically the most common form of lung cancer — non-small cell lung cancer. A nanodrug form of paclitaxel (Abraxane) has been approved by the FDA to treat certain patients with breast cancer since January 2005. In October 2012, the FDA approved nanoparticle paclitaxel for the treatment of advanced non-small cell lung cancer after a large clinical trial comparing nanoparticle paclitaxel with conventional paclitaxel as a treatment for advanced non-small cell lung cancer showed that the nanodrug benefited more patients (154).

The highly encouraging results of a recently concluded large clinical trial indicated that nanoparticle paclitaxel also significantly prolonged survival for patients with metastatic pancreatic cancer (155). Pancreatic cancer is one of the most deadly forms of cancer; most patients die within 12 months of diagnosis, and just 6 percent survive five years (1). With such a clear need for new treatment options, the breakthrough achieved with nanoparticle paclitaxel is providing new hope for patients like **Dr. Charles Haerter**.

### Mapping Cancer's Escape Route

For many patients with cancer, the first step in their treatment is to have their tumor surgically removed. In some patients, most commonly patients with breast cancer or melanoma, the surgeon also removes the lymph node or nodes to which the cancer is most likely to first spread to from the initial tumor. These lymph nodes are called sentinel lymph nodes. The presence or absence of cancer cells in these nodes helps determine the extent of the disease and provides information that is central to the development of the rest of the patient's treatment plan.



## Dr. Charles Haerter

Age 74  
Lake Havasu City, Ariz.

### Living with Metastatic Pancreatic Cancer Since 2008.

I was finally diagnosed with metastatic pancreatic cancer in March 2008, more than a year and a half after I had first experienced symptoms. I knew the outlook was not good and prepared to die. But I did not give up hope completely, and when my daughter-in-law heard about a clinical trial for pancreatic cancer that was having amazing results, I knew I wanted to give it a try. Within a month of receiving the trial drug Abraxane (a nanoparticle form of paclitaxel) I started feeling better.

I first experienced symptoms during the summer of 2006. I had several episodes of severe pain under my ribs on my right side. To me, as a physician, they seemed to be pretty typical gallbladder attacks. But two workups found no issues with my gallbladder and failed to identify a cause of my pain.

Later that year, I started experiencing pain in my lower left abdomen. I underwent all sorts of tests, most of them focused on my intestines. But one, a magnetic resonance cholangiopancreatography (MRCP), did image my pancreas, which looked normal. Because no one could come up with a better diagnosis, I was treated with anti-inflammatories in case I had inflammatory bowel disease.

The anti-inflammatories took away the pain, but I still didn't feel right. Then I started to lose weight and my energy went away.

By this time it was January 2008. I met with my family doctor, and he said he would get to the bottom of things. I had a CT scan, and there, in the tail of my pancreas, was what looked like a tumor about four or five centimeters in size. An endoscopic biopsy, which was performed at the Mayo Clinic in Arizona, several weeks later confirmed that it was pancreatic adenocarcinoma.

I was told that surgery was not an option because my cancer had spread to some of my lymph nodes and my liver, and that if I was lucky I might have one year left to live.

My daughter-in-law, who is a physician, was with us when I was told of the grim prognosis. She mentioned that she had heard, just days earlier, about a clinical trial that was going on at Scottsdale Healthcare for patients with metastatic pancreatic cancer. She had been told that the drug being tested, nanoparticle paclitaxel, was having dramatic effects and suggested this as a possible treatment for my cancer. As my endoscopic biopsy had been performed at the Mayo Clinic, I began my journey with nanoparticle paclitaxel in combination with a chemotherapy called gemcitabine (Gemzar), at the Mayo Clinic.

Almost immediately I felt a better well being. I was also optimistic that the treatment might add a few more years to my life. It has. It is now five and half years since my diagnosis.

During that time, I have been treated with nanoparticle paclitaxel on and off, mostly at the Mayo Clinic, but recently at Scottsdale, Ariz Healthcare, under the direction of Dr. Daniel Von Hoff. I have suffered from a variety of side effects that have meant that at times I have had to stop treatment with the drug. But each time I have restarted treatment, my cancer has responded. My pancreatic tumors have never disappeared completely, but they always shrink in size, and I feel as good as you can feel with pancreatic cancer.

The treatment I have received has been almost exclusively through clinical trials, and I have received the best care that anyone could have. But many doctors and members of the general public do not know about the clinical trials that are going on. We need to do a better job of educating people and getting them involved, because we need more people and more studies if we are to help more patients.

The successes of nanoparticle paclitaxel are spurring the development of other anticancer nanodrugs, and it is clear that this approach to drug delivery will become increasingly common in the future.

To identify the sentinel lymph nodes, patients are injected with a radioactive substance, a blue dye, or both. The surgeon then uses a device that detects radioactivity to find the sentinel node(s) and/or looks for lymph nodes that are stained with the blue dye. In March 2013, the FDA approved a new agent for locating lymph nodes in patients with breast cancer or melanoma who are undergoing surgery to remove sentinel lymph nodes. The agent, technetium Tc 99m tilmanocept (Lymphoseek), is a radioactive diagnostic imaging agent that was shown in two clinical trials to locate more sentinel lymph nodes in more patients compared with vital blue dye (156, 157). Further, technetium Tc 99m tilmanocept identified more sentinel lymph nodes that were subsequently shown by routine pathology to contain cancer cells. As a result, its use should improve post-surgery treatment decisions for patients who have breast cancer or melanoma.

### Clear Images with Lower Radiation Doses

Exposure to ionizing radiation is linked to the development of cancer (158). In the United States, the main source of ionizing radiation is a natural source: Radon gas. However, people are also exposed to ionizing radiation from man-made sources, predominantly medical equipment, treatments, and diagnostic agents.

A growing concern is the dramatic rise in the number of CT scans being performed for screening and diagnostic purposes (159). It has been estimated that the number of CT scans performed each year in the United States rose from three million in 1980 to 85 million by 2011 (160, 161). In 2011, approximately 11 percent of these CT scans were performed on children. Experts believe that children are particularly vulnerable to the effects of ionizing radiation, and a recent report projected that for every 4 million pediatric CT scans performed, almost 5,000 cancers will develop (162). However, the researchers also calculated that substantially reducing the top 25 percent of radiation doses would likely prevent almost half of those cancer diagnoses.

One approach to limit radiation exposure from CT scans is to develop new machines that use lower doses of ionizing radiation. In September 2012, the FDA approved one such machine, the Aquilion One Vision CT scanner that provides high-quality images using lower radiation doses than previous generation CT scanners (163). As technology continues to advance, progress in this area is expected to continue. When combined with educational programs to reduce the number of these procedures and to reduce radiation doses to only what is medically necessary, further decreases in cancer risk should be seen.

### Seeing the Wood Through the Trees: Improving Breast Cancer Detection

The rapid pace of technological innovation over the past few decades has been translated into a vast array of tools that have transformed the way that we detect and diagnose cancer. This arsenal of tools includes the machines that have enabled the United States to establish a population-based mammography screening program. Although early detection of breast cancer through regular mammography screening of women older than 40 has been credited with reducing the mortality rate for breast cancer (1), researchers have known for a long time that the greater the density of a woman's breasts, the less likely a cancer will be visible on a screening mammogram (164, 165). Moreover, women with extremely dense breasts have a more than fourfold increased risk of breast cancer (164).

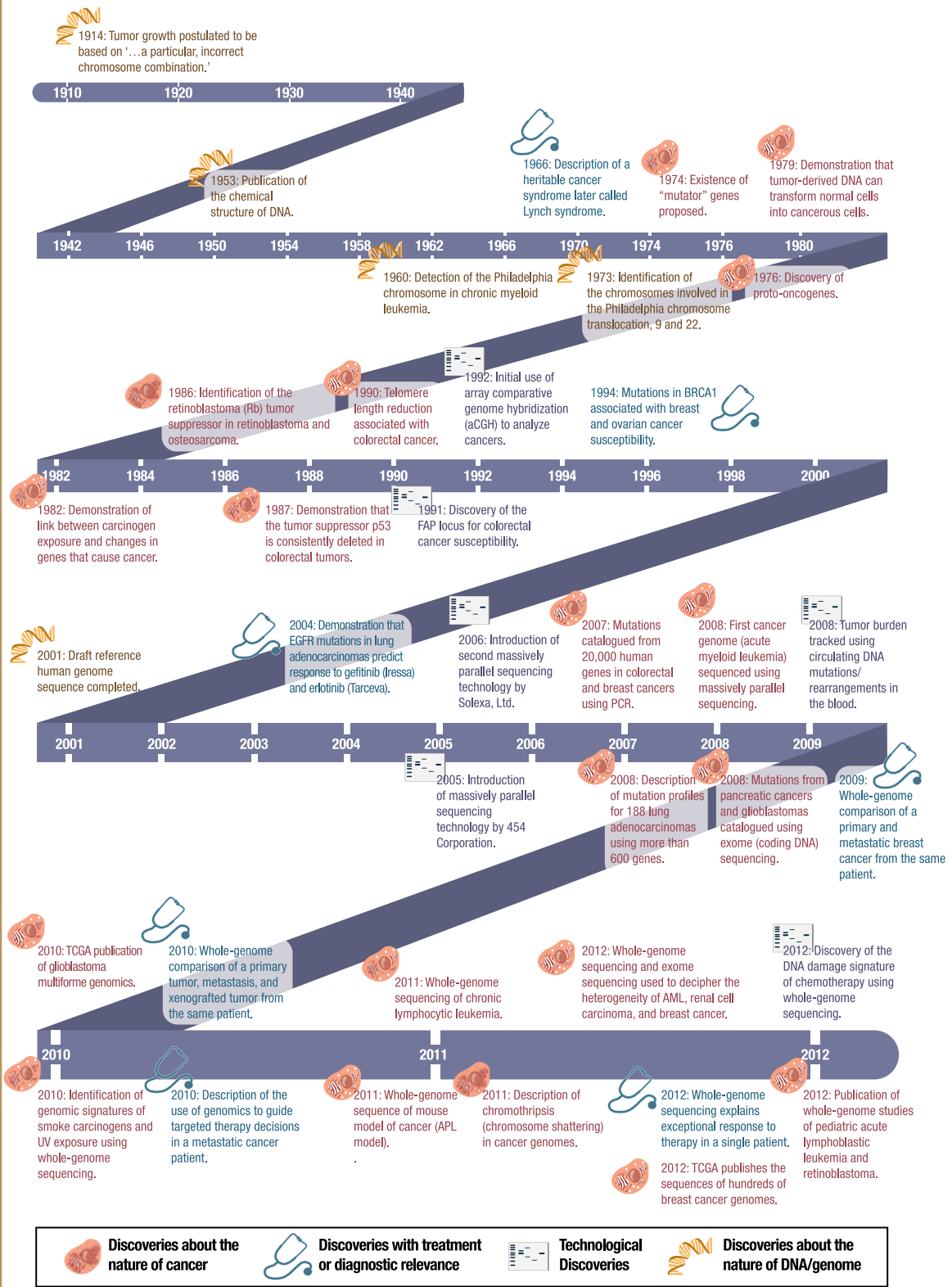
Ultrasound imaging can detect small tumors in dense breasts; however, hand-held ultrasound devices are not a routine part of population-based screening programs. The FDA's September 2012 decision to approve the use of the sono-v Automated Breast Ultrasound System (ABUS) in combination with a standard mammography for women with dense breast tissue should help to address this problem. The new device can automatically scan the entire breast in about one minute to produce several images for review. When tested in a clinical trial, the use of the sono-v ABUS in conjunction with standard mammography increased breast cancer detection in women with dense breasts, as compared to mammography alone (165).

The approval of the sono-v ABUS provides hope for more effective early breast cancer detection for the estimated 40 percent of women undergoing mammography screening who have dense breasts. However, as with all screening approaches, including standard mammography screening, there is the possibility that its use will lead to overdiagnosis and subsequent overtreatment (see **Prevention and Early Detection of Primary Tumors**, p. 28). Research to investigate this issue is vital to ensure that the public has confidence in this and other new screening approaches under development.

### Genomic Medicine

As mentioned earlier in this report, one of the greatest advances in cancer research was the discovery that cancer can be caused by permanent changes, or mutations, in the genetic material in a normal cell (see **Figure 6**, p. 12). Knowing that cancer arises because these mutations lead to protein abnormalities that disrupt normal cell behaviors has enabled researchers to develop anticancer drugs that target the

**Figure 16: The Long and Winding Road to Genomic Medicine.** (Legend on p. 59)



abnormal proteins and/or the disrupted cell behaviors. These molecularly targeted drugs are providing patients with some forms of cancer with less toxic and more effective treatment options, thereby realizing the promise of precision medicine.

Technological advances are making it possible to efficiently and cost-effectively read every unit, or base, of the DNA from a patient's cancer, and to compare it to the sequence of their normal cells (see **Figure 16**, p. 58). Widespread use of these new technologies has led to an explosion of genetic information about cancers of different types. One approach, known as whole-genome sequencing, compares the entirety of the DNA in a patient's normal tissue with that from their tumor. Initiatives using these new "massively parallel" sequencing technologies have identified all of the genetic changes within hundreds of samples of many types of cancer (see sidebar on **Large-Scale Genomic Initiatives**).

One message that is emerging from analysis of the genomic data is that there are about 140 genes that, when altered, can promote, or drive, the development of cancer (166). More significantly, these driver genes produce proteins that participate in perhaps only a dozen molecular networks (see **Figure 17**, p. 60). The fact that the same driver genes and networks are disturbed in different cancers is changing the way that researchers view and, more importantly, how clinicians treat cancer. Increasingly, cancer is viewed as a group of genetic diseases, defined not only by where they originate — in the brain, breast, liver, lung, etc. — but also by the genetic alterations that are driving their formation.

As cancers of different anatomical origins can be driven by similar genetic and molecular alterations, molecularly targeted drugs developed to treat cancer arising in one tissue can be repurposed as effective treatments for cancers with the same defect originating in a different tissue. For example, the HER2-

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**Figure 16: The Long and Winding Road to Genomic Medicine.** We now understand that many cancers are caused by genetic changes, or mutations, that lead to altered proteins and disruption of normal cell behaviors, and use this knowledge to develop anticancer drugs that target these proteins. But it was almost 40 years before the chemical structure of deoxyribonucleic acid (DNA) was published that Theodore Boveri first suggested that genomic abnormalities might cause cancer. Highlighted here are just some of the research milestones that have led to our current understanding of the genome's relevance to cancer development. As with all research, the more knowledge that is obtained, the more rapidly new discoveries can be made. In the area of genomic medicine, technology has been a tremendous catalyst for speeding these discoveries. The DNA strand symbol indicates discoveries about the nature of DNA and/or the genome; the cell symbol indicates genetic and/or genomic discoveries about the nature of cancer; the DNA blot symbol indicates technological breakthroughs; and the stethoscope symbol indicates research advances with treatment or diagnostic implications.

## Large-Scale Genomic Initiatives

Cancer is predominantly caused by changes, or mutations, in the genetic material in a normal cell. Analyzing the entirety of the DNA in cells from a particular form of cancer enables researchers to identify the genetic mutations that potentially drive that form of cancer. This in turn facilitates the development of anticancer drugs that target the resultant abnormal proteins.

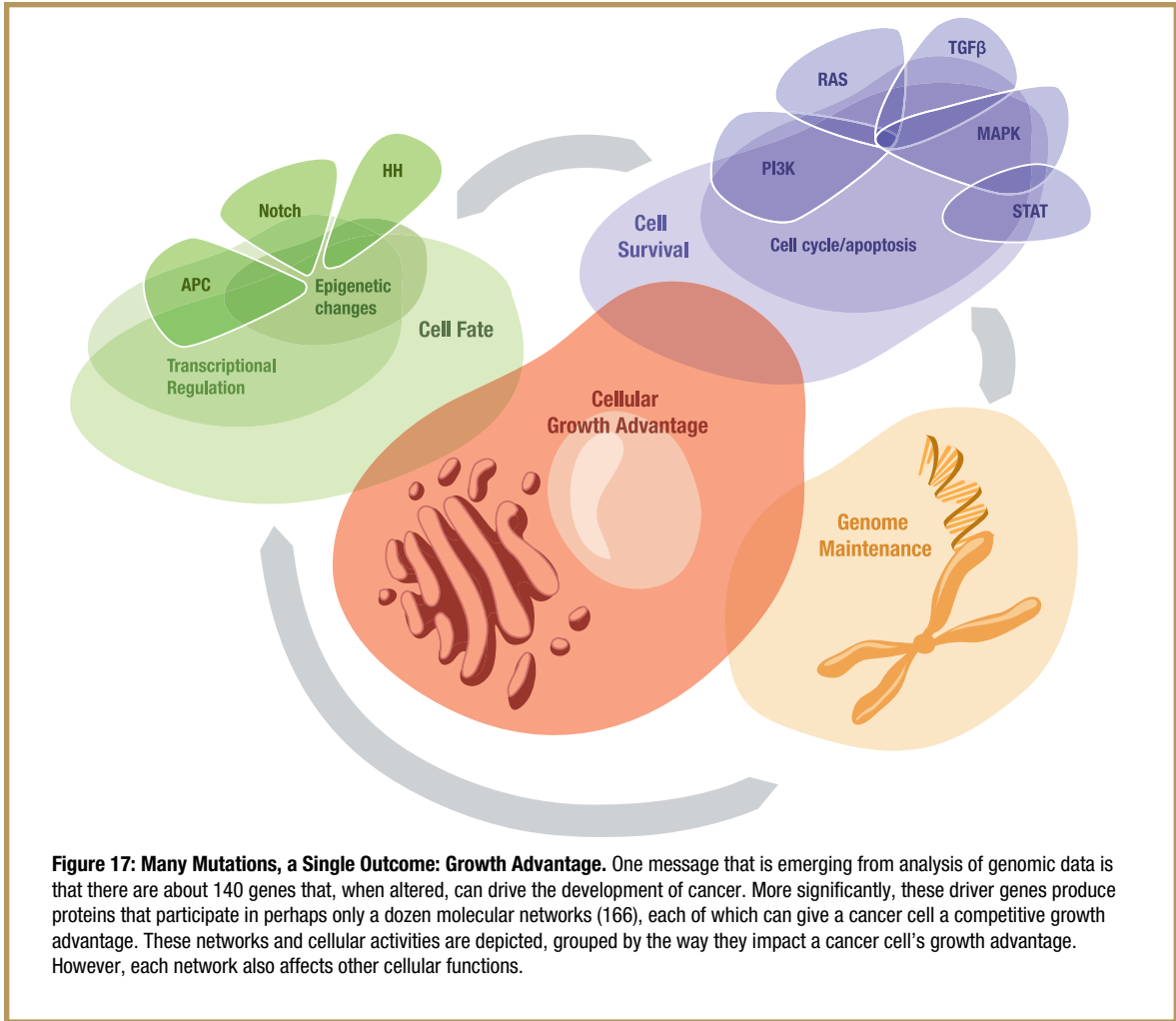
There are several ongoing, coordinated efforts to exploit whole-genome sequencing to comprehensively identify the genetic mutations in numerous different cancer types and subtypes. These initiatives include: The Cancer Genome Atlas (TCGA), International Cancer Genome Consortium (ICGC), and the St. Jude Children's Research Hospital–Washington University Pediatric Cancer Genome Project (PCGP).

The National Cancer Institute (NCI) and the National Human Genome Research Institute (NHGRI) launched TCGA ([cancergenome.nih.gov](http://cancergenome.nih.gov)) in 2006. Researchers involved in this initiative are charting the genomic changes in more than 20 types or subtypes of cancer. For each form of cancer being studied, tumor and normal tissues from hundreds of patients are analyzed. Data generated through TCGA are freely available and widely used by the cancer research community.

Launched in 2008, the ICGC ([icgc.org](http://icgc.org)) comprises research groups around the world, including some from TCGA. This international effort aims to harmonize the many large-scale genomic projects underway by generating, using, and making freely available common standards of data collection and analysis. Its goal is to identify the genetic changes in 50 different types or subtypes of cancer, and it currently has 53 project teams studying more than 25,000 tumor genomes. For each form of cancer being studied, tumor and normal tissues from approximately 500 patients are analyzed. Data generated by ICGC project teams are freely available and widely used by the cancer research community.

St. Jude Children's Research Hospital, in Memphis, Tenn., and Washington University, in St. Louis, Mo., joined forces in 2010 to sequence the genomes of both normal and cancer cells from more than 600 children with cancer. The PCGP ([pediatriccancergenomeproject.org](http://pediatriccancergenomeproject.org)) is the largest investment to date aimed at understanding the genetic origins of childhood cancers.

The data generated by these initiatives are already reshaping our definition of cancer. We now increasingly view cancer as a group of diseases defined not only by the anatomical site from which they originate, but also by the genetic alterations that are driving their formation. This new knowledge is rapidly advancing precision medicine. As more projects are completed in the coming years, we will undoubtedly see further advances that benefit patients.

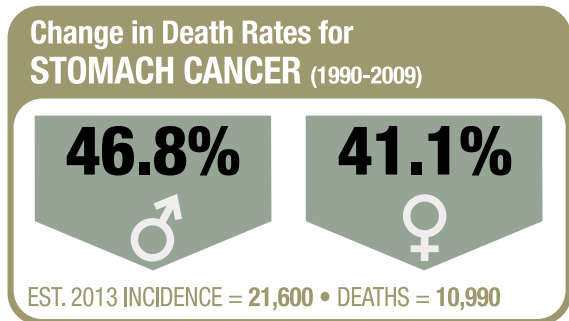


targeted therapy trastuzumab was originally developed to treat patients with breast cancers that overexpress the HER2 protein due to the presence of extra copies of the HER2 gene and later shown to prolong survival for patients with stomach cancer harboring extra copies of the HER2 gene (167).

Currently, however, our use of large-scale genomic data is limited to the research setting. Here, it is guiding the development of new cancer drugs, directing the repurposing of established molecularly targeted therapies, and aiding clinical researchers in assigning patients, like **Carol Weinbrom**, to the most appropriate therapies and clinical trials.

Recently, two independent large-scale genomic studies provided insight that could benefit some patients with breast cancer that tests negative for HER2 gene amplification (168, 169). These patients are considered ineligible for treatment with HER2-targeted therapies like trastuzumab. However, the large-scale genomic analyses found that some tumors that test negative for HER2 gene amplification harbor a mutation in the

HER2 gene that causes their HER2 proteins to be overactive in the same way that HER2 gene amplification does, suggesting that they might be sensitive to HER2-targeted therapies. Thus, a clinical trial has been launched to evaluate whether the investigational HER2-targeted therapy neratinib is a good treatment option for patients with metastatic breast cancer harboring HER2 gene mutations but not amplifications.





## Carol Weinbrom

Age 67  
York, Pa.

### Living with Metastatic Breast Cancer Since 2001

I am in my 12th year of treatment for metastatic breast cancer. Although I have been in treatment constantly since my diagnosis, I have lived, and continue to live, a full and productive life. In 2012, I had my tumor genetically profiled. This empowered me. It enables me to search for clinical trials of new drugs that might keep me alive with minimal toxicity so that I can continue enjoying life.

My journey with cancer began in 2001 when I went to my general practitioner because I was tired, so tired I was having trouble completing simple tasks. He told me he felt an enlarged liver and sent me for a CT scan. The scan revealed tumors in my liver. At the time they thought it was liver cancer, but biopsies showed that it was not. It was breast cancer. I was metastatic from day one.

My first thought was: How long do I have to live? Is there any chance of survival? I felt I had to say goodbye to my future.

But the reality is that I joined a vibrant group of people living with metastatic breast cancer. You might not recognize us, we may look just like you, we are not cancer survivors, we are surviving with cancer, constantly receiving treatment. In essence, we live two parallel lives.

For me, for the first two years after diagnosis, one life was a series of chemotherapies that reduced levels of tumor markers in my blood. The other was a full-time job, a busy home life, and family obligations.

At the end of those two years, my tumor markers had dropped to levels found in healthy women, and CT scans showed no evidence of disease. I was placed on anti-hormone therapy, exemestane (Aromasin), and for the next five years I lived an almost normal life.

At that time, a tumor again appeared in my liver. After radiofrequency ablation of the tumor and six months taking capecitabine (Xeloda), my tumor marker levels were once again normal, and I went back on an anti-hormone therapy, this time fulvestrant (Faslodex).

Then, in the summer of 2010, several tumors were detected in my liver. I started back on a series of chemotherapies. First, I received carboplatin and a nanodrug called Abraxane. Then, when that drug combination failed, I received gemcitabine (Gemzar). But my

body crashed and I needed several platelet and other blood cell transfusions.

To my community oncologist, I added an oncologist at a regional cancer center. I was placed on tamoxifen, but my disease progressed, so I changed to eribulin (Halaven). It was a great drug for me and my tumor markers almost reached normal levels. However, I had to stop taking eribulin in December 2012, because my platelet and blood cell counts plummeted.

That is when I identified a research oncologist and agreed to the genetic analysis of my tumor. I knew that I had the option of going on with chemotherapy or looking for more targeted drugs. I wanted more targeted drugs, and I knew that genetic analysis was a way to get to them.

The results of the genetic analysis indicated that everolimus (Afinitor) might be effective against my cancer. Unfortunately, it wasn't. This frustrated me because, for the first time in my treatment, I had something that was telling me a drug should work for me but it wasn't. I thought: What am I missing in the analysis?

My research oncologist explained that currently, genetic analysis is not all encompassing because knowledge today has its limits. He also said that our knowledge is rapidly expanding and that in time genetic analysis will give a more comprehensive picture of tumors.

Although genetic analysis failed to identify a drug that benefited me, the power that it gave me was priceless, and I would recommend it to anyone in my position.

I am currently receiving an investigational drug through a phase Ib clinical trial. It is one of very few options left to me. The reality is that I am at the end of approved treatments. I rely on investigational drugs and the researchers who are identifying new ones.

To ensure that drugs are constantly entering the pipeline, researchers need a dependable source of funding. What I don't understand is why research into cancer, and all other diseases, is not automatically funded at a steady level by the government. As a metastatic breast cancer patient out of approved therapies, I feel I have to beg for the dollars to support the research behind my next drug. I don't think I, or anyone, should have to beg.



## Molecularly Informed Clinical Trials

Experimental treatments sometimes yield exceptional responses in a fraction of the patients in which they are tested, yet have no effect at all in others. What accounts for these differences, and how can scientists learn from them in order to target the right drug to the right patient?

Decades of research have shown that there are more than 200 separate types and subtypes of cancer and that, even within the same type or subtype of cancer, there may be considerable variability at the genetic and molecular levels. Armed with this information, investigators are developing drugs that attack cancers by honing in directly on the genetic and molecular abnormalities that drive them. To test these drugs efficiently, researchers are exploring novel approaches to designing clinical trials.

Clinical trials have historically focused on testing whether or not a drug affects cancers at a particular organ site — say cancers of the breast or colon. A new approach to clinical trial design is to examine the effect of a particular therapeutic agent on a particular genetic or molecular abnormality regardless of the type of cancer in which it occurs. For example, in so-called “basket studies”, a drug targeting a particular molecular abnormality, say a BRAF abnormality, may be tested on colorectal cancer patients, lung cancer patients, and ovarian cancer patients who have the BRAF gene mutation that generates the cancer-driving abnormality. Within a given trial, patients with the different types of cancer can be grouped into separate study arms, or “baskets.” This allows researchers to separately analyze the responses of patients with each type of cancer as well as to assess the impact of the drug on all of the patients as a group. While researchers have used this approach on a relatively small scale, the National Cancer Institute has recently announced plans for the MATCH trial, which would pair up to 1,000 people with a variety of cancers to therapies that target the specific mutations found in their tumors.

“Umbrella” trials are another approach that researchers are exploring as a possible way to improve the efficiency of clinical trials. Whereas in basket studies researchers test the effect of a single drug, on a single mutation in a variety of cancer types, umbrella studies are designed to test the impact of different drugs on different mutations in a single type of cancer. In the BATTLE umbrella trial, for example, researchers recruited non-small cell lung cancer patients, genetically profiled their tumors to determine which mutations they had, and then assigned them to receive a particular drug expected to target their mutations.

Basket and umbrella studies represent novel approaches to testing targeted therapeutics. Both types of studies have the potential to accelerate the drug development process so that the right therapies can quickly be delivered to the right patients.

Such genomically informed clinical trials are likely to become more common in the future. It is hoped that such trials will not only accelerate the translation of scientific discoveries into new therapies, but will also increase the number of patients who benefit from new and existing molecularly targeted drugs. To accomplish this, several new collaborative, genomic-based approaches to anticancer drug development and clinical trials are being planned (see sidebar on **Molecularly Informed Clinical Trials**).

In addition to guiding clinical trial design, researchers are beginning to use large-scale genomic analysis to help understand why a small number of patients often respond in otherwise failed clinical trials. In many clinical trials testing anticancer drugs, not enough patients benefit from the drug to support its further development, although there are often exceptions: rare patients who gain enormous benefit from the drug under investigation. These patients are referred to as rare or exceptional responders. Genomic studies that focus on explaining why these patients responded while the majority of patients did not are sometimes referred to as “n-of-1” studies.

The promise of exceptional responder studies was highlighted recently when researchers performed large-scale genomic analysis on a tumor sample from an exceptional responder in a failed clinical trial testing the drug everolimus (Afinitor) as a treatment for metastatic bladder cancer (170). They identified a mutation in a gene called TSC1 that was of interest because a nonfunctional TSC1 protein would make cancer cells more dependent on the cellular pathway that everolimus shuts down. Further analysis revealed that TSC1 was mutated in several other patients in the clinical trial, including two patients who had minor responses to everolimus. This finding may resurrect everolimus as a potential treatment for bladder cancer, but only for patients with disease harboring mutations in the TSC1 gene.

As we move further into the era of precision medicine, it is evident that large-scale genomic analyses will be an essential catalyst for further progress against cancer in both the research setting and the clinic.

### Change in Death Rates for URINARY BLADDER CANCER (1990-2009)

3.8%



10.7%



EST. 2013 INCIDENCE = 72,570 • DEATHS = 15,210

# On the Horizons

## In this section you will learn:

- **Combinations of molecularly targeted therapies** based on cancer biology are likely to become part of the standard of cancer treatment in the near future.
- Small, synthetic **noncoding nucleotides** (DNA or RNA) are being actively investigated for their potential to precisely eliminate the effects of disease-causing genetic mutations.

Cancer research has taught us that the collection of diseases we call cancer is complex at every level and that it is adaptive, continually developing ways to evade even our most precise treatments. It is clear, however, that the more we understand about the ways in which cancer arises and adapts, the better we are at treating it. For example, we previously thought that the only unique characteristic of cancer cells were their ability to rapidly divide. As such, we treated cancer patients with drugs that target all dividing cells, even normal ones. Now, we can identify specific genetic alterations within cancer cells that can fuel their division, and develop drugs that precisely target the molecular abnormalities that arise as a result of these modifications.

As we continue to pursue a comprehensive understanding of the biology of cancer at all stages — the root causes of its initiation, growth, and metastasis — and at all scales, from genes, to molecules, to cells, to humans, novel strategies for making further strides in the prevention, detection, diagnosis, and treatment of cancer will appear on the horizon. Regardless of what these next breakthroughs against cancer are, they will surely come from a convergence of scientific disciplines, a diversity of scientific and health care practitioners, as well as a variety of approaches. A problem as complex as cancer will undoubtedly require a multifaceted solution.

## The Near Horizon

As discussed throughout this report, cancer cells are rife with genetic alterations that give them a competitive growth advantage when compared to noncancerous cells. Cancer

research has provided us with the ability to identify these alterations and to develop novel and effective medicines that target cancer cells with some of them. Due in large part to the presence of many different alterations within a patient's cancer, however, cancers can adapt and fuel their growth through an alteration other than the one blocked by a given medicine. This leads to continued or worsened disease.

Near-term breakthroughs against cancer are likely to come from simultaneously blocking the alterations that drive the primary and adaptive growth advantages, forcing the cancer to stop growing and ultimately die. This approach has been successfully used for decades using combinations of a variety of cytotoxic, or nontargeted, chemotherapies, but these have lacked the precision of our current medicines and often are highly toxic. Within a few years we are likely to see many more clinical trials evaluating molecularly targeted therapies in rational combinations determined by our enhanced understanding of cancer biology. In fact, some early trials testing rational combinations of molecularly targeted therapies are underway. For example, the combination of dabrafenib and trametinib, which block different components of the same cancer-driving signaling network, is already showing promise as a treatment for some patients with metastatic melanoma (150) (see **Two Drugs: One Cancer-driving Pathway**, p. 53). Likewise, a combination of two immunotherapies that target different immune checkpoint proteins, ipilimumab and nivolumab, are showing early benefit for patients with advanced melanoma (115) (see **Releasing the Brakes on the Immune System**, p. 38).

This approach, however, requires that we understand enough about the underlying biology of cancer to be able to accurately predict the alternative growth advantages most likely to be used by the cancer. The knowledge required to do so will come from a variety of sources including whole-genome sequencing, patient-derived xenograft testing (see sidebar on **Patient-derived Xenografts**), and predictive mathematic modeling of cancer behavior using systems biology and evolutionary theory.

Even armed with this deeper understanding of cancer biology, much work needs to be done to determine the order, duration, and dosing of the combination of anticancer agents being used. Here again, mathematical modeling and systems biology approaches will be critical to narrowing the nearly infinite

## Patient-derived Xenografts

A recent advance in personalized cancer medicine is the use of mouse avatars, or patient-derived xenografts, to help identify which drug or drug combinations are most likely to be effective for an individual cancer patient. While this remains far from being widely used, its promise has been clearly demonstrated (171).

Patient-derived xenografts are generated by implanting portions of a patient's tumor into several mice. A large number of potential therapies can then be tested on the mice for their ability to destroy the patient's tumor before they are given to the patient. This pretreatment screening increases the likelihood that a given treatment plan will benefit the patient, and eliminates exposure to therapies from which the patient is unlikely to benefit.

In one of the first clinical studies of treatment guided by patient-derived xenografts, avatars were created for 14 patients with advanced cancers nonresponsive to current standard-of-care therapies. In this study, avatar screening successfully identified an effective treatment strategy for 12 of the patients. Importantly, these treatment strategies would not have been offered to these patients without the avatar screening. Moreover, as a result of the drugs identified through the avatar screening process, one of the patients who had advanced pancreatic cancer was disease free more than six years after diagnosis (172).

In addition to their clinical potential, patient-derived xenografts are also being used in the research setting to enhance our understanding of cancer biology and to accelerate drug development. For example, some researchers are starting to use patient-derived xenografts to help them select which drugs should be evaluated in clinical trials and for which patient groups.

Despite their promise, there are many challenges to using patient-derived xenografts. First and foremost, they are difficult to generate, and the success rate for implanting human tumors in mice is low. Second, it takes more than six months to generate patient-derived xenografts and screen potential therapies. Most patients do not have that much time. Last, to treat one patient, many avatars have to be generated, which costs tens of thousands of dollars. However, if these obstacles are overcome, patient-derived xenografts may help many more patients in the future.

permutations into a manageable subset that can be tested in clinical trials. Perhaps one of the most intriguing areas of combination therapy will be adding the new immunotherapies to radiotherapies, chemotherapies, and molecularly targeted therapies to enhance clearing of the tumor by the immune system (see **Special Feature on Immunotherapy**, p. 38).

We are just beginning to mine our cache of existing tools and drugs to develop rational combinations that are likely to provide better and more durable cancer responses than any of the agents alone. Continued research will speed these breakthroughs within the next few years.

## The Distant Horizon

Of the nearly 3 billion bases in the human genome, only about 1.5 percent code for the various proteins a cell uses to function. Just more than a decade ago, researchers made the important discovery that some of the remainder of the genome codes for molecules called noncoding RNAs, which naturally regulate gene usage and therefore the production of proteins.

Since that discovery, small, synthetic noncoding RNAs and DNAs have become vital tools in research laboratories worldwide. Researchers are also exploring the possibility that their ability to dampen gene usage and protein production can be exploited for patient benefit. Unfortunately, the use of synthetic noncoding nucleotides (DNA or RNA) in this way has been hampered by our inability to effectively deliver them to a patient's cancer.

When combined with whole-genome sequencing, the clinical use of small, synthetic noncoding nucleotides could potentially revolutionize cancer treatment. Here, the identification of the exact mutations fueling an individual's cancer would be identified through whole-genome sequencing. An anticancer therapeutic composed of small, synthetic noncoding nucleotides would then be prepared to potentially eliminate the abnormal protein(s) produced by these mutations, negating the competitive growth advantage of the cancer cells.

Because of the potential power of small, synthetic noncoding nucleotides, this is, and has been, a very active area of research. The infrastructure and technology to produce such therapeutics are already in place, and in some cases in early clinical testing. Given our rapid pace of discovery across all scientific sectors, it is likely that anticancer therapies based on small, synthetic noncoding nucleotides will one day benefit patients. Continued progress is incumbent upon continued research and investment in this area.

# What is Required for Continued Progress Against Cancer

## In this section you will learn:

in addition to providing sustained increases in funding for biomedical research, we can accelerate the pace of progress against cancer by:

- **advancing** regulatory science and policy;
- **increasing patient participation** in clinical trials;
- **enhancing** the cycle of research through the adoption of electronic health records;
- **improving the quality and consistency of biospecimen resources;** and
- **cultivating a highly skilled and diverse research workforce.**

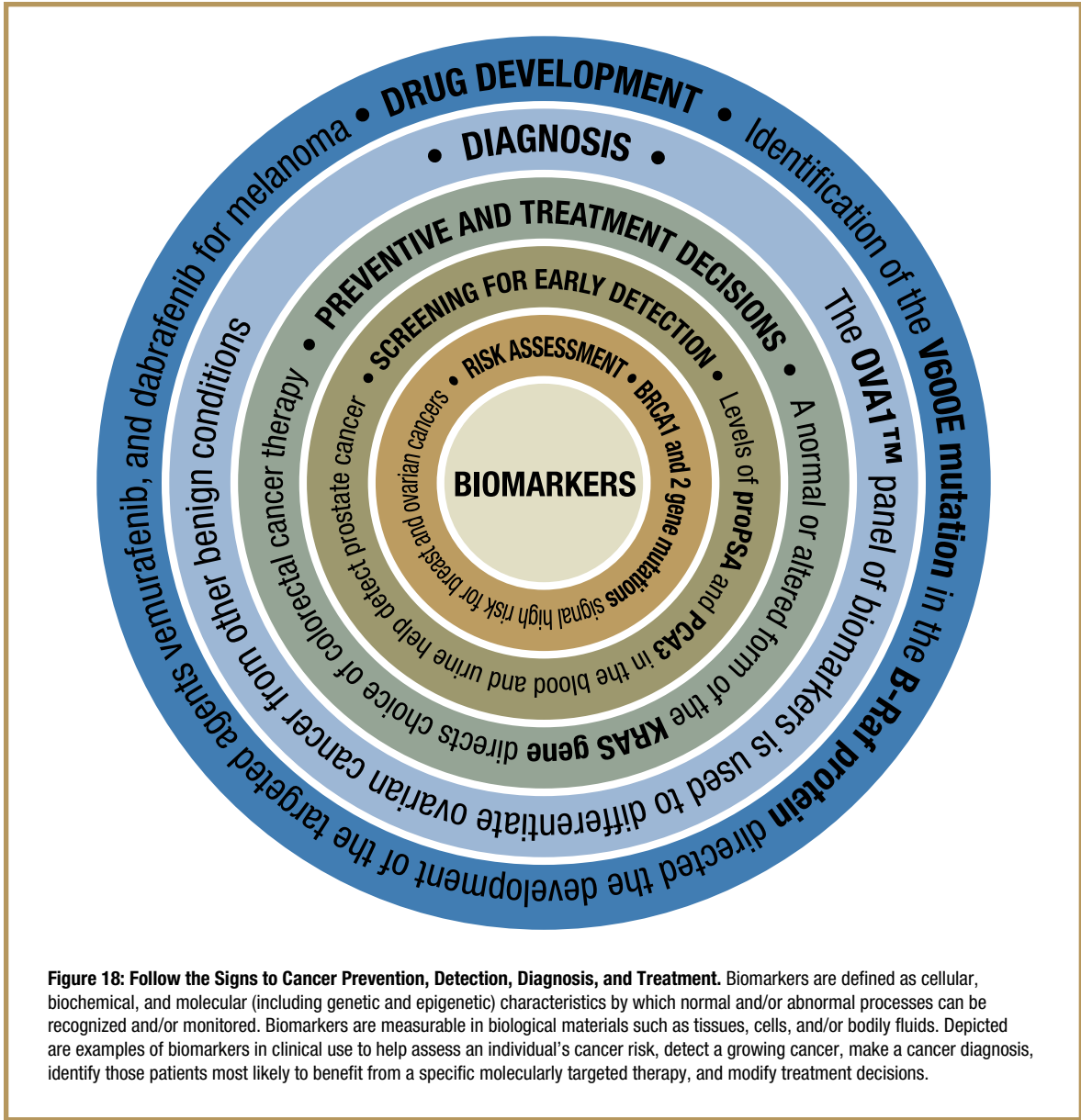
This report celebrates the extraordinary contributions to preventing, detecting, diagnosing, and treating cancer made by biomedical research. It also provides a window into a future in which cancer care will be transformed by the discoveries made in laboratories throughout the world. To fulfill the promise of these discoveries we must make cancer research a national priority. This includes investing in the talent, tools, and infrastructure that drive innovation, as well as advancing policies that enable researchers to develop a more comprehensive understanding of cancer and to translate that knowledge for the benefit of patients.

Increased funding for cancer research from the federal government and other sources is clearly required if we are to continue to pursue a comprehensive understanding of the biology of cancer (see **Funding Cancer Research and Biomedical Science Drives Progress**, p. 69). But how we conduct the research matters. Innovative efforts in strategic areas are needed if we are to become more efficient and productive, and here we highlight some of these opportunities.

## Advancing Regulatory Science and Policy

As cancer research advances, so must the tools, standards, and techniques for assessing the safety and efficacy of all new products used to prevent, detect, diagnose, and treat cancer. This is particularly important in the realm of precision medicine, where research and development methods are continuously being refined to incorporate advances in basic and clinical research.

For example, it will be necessary to develop improved approaches to identifying, qualifying, and validating biomarkers (see **Figure 18**, p. 66), particularly since their use is becoming increasingly important for developing effective diagnostic tools and therapies and making treatment decisions. Likewise, advances in clinical trial design are needed if we are to test drugs more rapidly and efficiently. This is particularly important for the evaluation of molecularly targeted drugs that attack cancers by honing in directly on the genetic and molecular abnormalities that drive them (see **sidebar on Molecularly Informed Clinical Trials**, p. 62). To advance regulatory



science and policy, the FDA must have the resources to recruit and retain highly qualified staff, as well as develop new tools and techniques. They must also have the means to fully engage with the broader scientific community in discussion about areas of scientific progress so that the work of this important agency will benefit from the latest advances in the field. Likewise, these interactions also benefit the broader scientific community by providing it with a better understanding of regulatory policies, facilitating the translation of discoveries into new and improved therapies.

### Engaging Patients in Clinical Research

Clinical studies, particularly clinical trials, are a key component of cancer research (see **sidebar on The Virtuous Cycle of Biomedical Research**, p. 9) because they enable researchers to demonstrate that therapies showing promise in the laboratory are safe and effective for use in people. Typically, researchers conduct randomized clinical trials wherein experimental interventions are tested against the current standard of cancer care in patients and, in some cases, healthy volunteers. Although patient participation in

these studies is critical, fewer than 5 percent of adult cancer patients participate in a clinical trial (173). An even smaller fraction of patients from specific subgroups, like the elderly, women, racial and ethnic minorities, and people living in rural areas, participate in clinical trials, which leads to a lack of understanding of whether a drug is safe and effective in these populations. Low participation can slow the progress of clinical trials and delay the development of new therapies.

If we are to speed the translation of cancer research discoveries into new treatments, it is essential that all stakeholders work together to overcome the obstacles that discourage people from participating in clinical research studies. These obstacles may include a lack of information about the clinical research process, lack of awareness of studies for which patients are eligible, concerns about adverse side effects, the cost and quality of care, and a mistrust of the research establishment. Logistical challenges such as lack of transportation to and from distant trial sites may also make it difficult for otherwise willing volunteers to participate. To overcome these obstacles it will be important to improve outreach to patients, researchers, health care providers, policymakers, and the general public with the goal of providing accurate information about the clinical research process and the value of public participation in research. These groups must also work together to identify and implement solutions to the barriers that hamper research participation.

## Integrating Research and Patient Care

Cancer research is conducted in many places and in many ways (see sidebar on **The Virtuous Cycle of Biomedical Research**, p. 9), from studying cells in dishes in laboratories to testing new drugs through clinical trials. Regardless of the form that it takes, research involves generating, compiling, and analyzing information. The adoption of electronic health records (EHRs) is making it possible to gather data about what works best and for whom during the routine care of patients in everyday clinical settings. In this way, research and clinical care are increasingly becoming integrated. When fully implemented, a national EHR system will enable researchers to use data gathered in the clinic to answer pressing scientific questions and generate new research hypotheses. It will also help clinicians to deliver higher quality and more rapid care that is consistent with the latest research findings. To make this vision a reality, it is important to continue to promote the development of infrastructure and standards that enable the capture, aggregation, and analysis of information important to patients, clinicians, and researchers alike. Further, policies need to be developed and implemented to protect participant privacy and respect their informed consent regardless of how their information is collected or used.

## Improving Biospecimen Repositories

Much of our current understanding of cancer biology comes from studying tumor samples and other “biospecimens” that have been provided by patients. Such specimens will continue to be a critical component of cancer research and biomedical science. Unfortunately, many of the biospecimens available today are not suitable for use in research for a variety of reasons. Chief among these are an absence of standards in the collection, preparation, and/or storage of biospecimens, and an insufficient amount of accompanying clinical data. Studies using poor-quality biospecimens may yield inconclusive or erroneous results. Therefore, improving the quality and consistency of biospecimen resources is a top priority in cancer research. The research community must establish and adopt universal standards for collecting, annotating, cataloguing, and storing biospecimens, and the policies and infrastructure must be developed to enable more researchers to access these samples and the data generated through their use.

## Cultivating a Highly Skilled and Diverse Cancer Research Workforce

Continued progress against cancer depends on cultivating a highly skilled and diverse research workforce. Unfortunately, a lack of funding is jeopardizing our ability to attract students to research and driving established investigators out of the field (see **Funding Cancer Research and Biomedical Science Drives Progress**, p. 69). The current research environment poses difficulties for all scientists, but the challenges are particularly acute for young investigators (174).

It is especially difficult to recruit and retain scientists from historically underrepresented groups. A report by the NIH shows that while individuals identifying as Latino or Hispanic comprised 16.3 percent of the U.S. population in 2010, they accounted for a mere 3.5 percent of NIH principal investigators (175). Likewise, African-Americans, who made up 12.6 percent of the U.S. population in 2010, comprised only 1.1 percent of NIH-funded principal investigators. Although the reasons for these disparities are complex and multifaceted, one thing is clear: Innovation is driven by diversity of perspectives. By harnessing the scientific potential of people from all backgrounds and communities, we can foster a wider range of scientific ideas and accelerate the pace of progress against cancer.

In addition to providing the resources to recruit and retain talent to science, we must equip our workforce with the knowledge and skills to be able to conduct 21st century cancer research. This means continuing to provide world-class training

in basic, translational, and clinical research; ensuring trainees have access to cutting-edge tools and techniques; ensuring all researchers can participate in the latest scientific meetings and conferences; and cultivating the skills they will need to succeed in the interdisciplinary research teams that have become commonplace. Researchers across the entire biomedical research enterprise must also have access to professional development resources and support, including access to effective mentors, training in laboratory management, opportunities to hone their grant- and manuscript-writing skills, and exposure to the breadth of career opportunities in the relevant sciences.

# Funding Cancer Research and Biomedical Science Drives Progress

## In this section you will learn:

- Why Congress must make **funding cancer research and biomedical science a national priority**; and
- The future of the biomedical research enterprise is **threatened by sequestration** and a declining research budget.

As a direct result of past federal investments in the NIH (see sidebar on **The NIH**, p. 70), incredible progress has been, and continues to be, made against cancer. These advances are the result of dedicated efforts across all sectors of the biomedical research enterprise to continue to make research count for patients. As a testament to this progress, the FDA approved 11 new drugs for treating cancers, three new uses for previously approved anticancer drugs, and three new imaging technologies between Sept. 1, 2012, and July 31, 2013 (see **Table 1**, p. 4).

However, continued progress is under threat, and a new level of commitment by Congress to increase funding for the NIH will be required if we are to accelerate the pace of progress against cancer and meet the challenges described earlier in this report.

## Funding Cancer Research and Biomedical Science Saves Lives and Boosts the Nation's Economy

The federal government, through the NIH, is the primary investor in basic biomedical research (see sidebar on **The Virtuous Cycle of Biomedical Research**, p. 9). The knowledge gained through this research is essential to the entire biomedical science enterprise and a key driver of late-stage research, which is predominantly funded by the private sector.

Within the NIH, the NCI is the main funder of cancer research. NIH- and NCI-funded research has driven significant advances in our understanding of the biology of cancer and our ability to prevent, detect, diagnose, and treat it. These advances have significantly reduced the burden of cancer and transformed the lives of a growing number of cancer patients, including the 13.7 million cancer survivors estimated to be living in the United States in 2013. This remarkable progress would not have been possible without the long-standing, bipartisan commitment of our nation's policymakers to invest in biomedical research through the NIH.

In addition to improving the health of the nation, investment in the NIH boosts our nation's economy. NIH funding supports nearly half a million jobs nationwide (180). In fact, the funding that local areas receive has a positive ripple effect throughout those communities. NIH funding generated more than \$62 billion in economic activity in the United States in 2011 (181). As our nation continues to recover from a long recession and a period of high unemployment, sustaining a proven economic generator is smart fiscal policy.

## Human Genome Sequencing

In 2012, **human genome sequencing** and related activities directly and indirectly generated:

- \$65 billion in U.S. economic output;
- \$31 billion toward 2012 U.S. gross domestic product;
- \$19 billion in personal income; and
- 152,000 jobs.



## The NIH

The National Institutes of Health (NIH) is the largest source of funding for biomedical research in the world. It is responsible for seeking fundamental knowledge about the nature and behavior of living systems and the application of that knowledge to enhance public health, lengthen and improve the quality of life, reduce the burden of illness and disability, and save lives. In fact, due in large part to NIH research, the average life expectancy in the United States today is nearly 79 years, almost 30 years longer than it was in 1900, and the proportion of older people with chronic disabilities has dropped by nearly one-third over the past 25 years (176).

The agency carries out its mission to support lifesaving medical research by awarding competitive research grants to more than 300,000 scientists working at more than 2,500 universities, medical schools, medical centers, teaching hospitals, research institutions, and small businesses across the country. In fact, at least 80 percent of NIH's \$29 billion budget is provided to these independent researchers who are working in communities in every state (176).

Additionally, about 10 percent of the NIH budget supports projects conducted by nearly 1,200 principal investigators (177) and 5,000 research trainees in its own internal laboratories (178), most of which are on the main campus of the NIH in Bethesda, Maryland. Bethesda is also the home of the NIH Clinical Center, the largest hospital in the world dedicated entirely to clinical research.

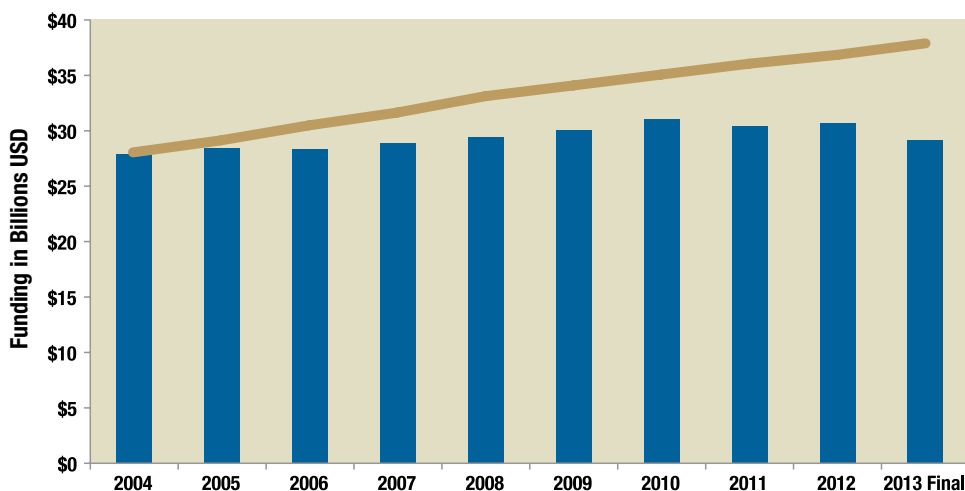
Funding for all NIH research programs generates scientific discoveries and fuels new economic activity and employment in the communities that receive these funds. In 2011, NIH research funding led to the creation of 432,094 jobs and generated \$62.13 billion in new economic activity across the country (179).

## Sequestration and a Declining Research Budget Threaten the Future of our Nation's Health

In the late 1990s, following a period of stagnant budgets for medical research, Congress and the administration made a bipartisan, forward-thinking decision to double the NIH budget over a five-year period. Unfortunately, in the 10 years since the doubling ended in 2003, the NIH budget has been steadily shrinking because the amount of funding provided to the agency each year has been less than what is needed to keep pace with biomedical inflation (see **Figure 19**). This has effectively decreased the NIH's ability to fund lifesaving research.

In addition to this lost purchasing power, on March 1, 2013, outright budget cuts known as sequestration further reduced the NIH budget. Sequestration dealt a 5.1 percent cut to the agency, slashing its budget by \$1.6 billion. At the reduced fiscal year (FY) 2013 funding level of \$29 billion, the NIH is now funding the lowest number of research projects since FY 2001 (see sidebar on **Life Under Sequestration**, p. 71).

The impact of sequestration on the NCI was a commensurate cut of \$293 million. These cuts have ramifications across the research spectrum — reducing the number of promising grant proposals that can be funded, potentially leaving the next cancer therapy or cure on the cutting room floor. Furthermore, these cuts impact existing cancer research projects and cancer centers, where critical “bench-to-bedside” research and care take place.



**Figure 19: Effective Losses with a Significant Impact.** The biomedical research and development index (BRDPI) reflects the rising cost of personnel, supplies, and equipment needed to conduct biomedical research. In the past decade, the National Institutes of Health (NIH) budget has not kept pace with the BRDPI. As a result, the NIH has effectively lost approximately 20% of its ability to fund lifesaving research (178). The blue bars represent the appropriated funds; the gold line is the calculated BRDPI-dependent increase.

## Sequestration

**Sequestration** will result in a \$19 billion reduction to the NIH budget by 2021.

These cuts also reduce the number of patients who can enroll in NCI-funded clinical trials. Such trials are required for promising new treatments to move forward to the next phase of development and are often the only hope for patients with advanced cancers who have exhausted all approved treatment options.

Unless Congress takes action to find a balanced approach to deficit reduction and change the present fiscal course, the multiyear, reduced federal spending caps mandated by sequestration will result in a \$19 billion reduction to the NIH budget by 2021. This places the entire biomedical research enterprise at a crisis point, and the present trajectory is simply unacceptable.

Especially concerning is that these cuts to the NIH are occurring at a time when the potential for accelerating the translation of discoveries in cancer research into progress against cancer has never been more promising. As a result of declining budgets, the pace of discovery will slow and breakthroughs that could have led to new therapies will be delayed.

Not only is the overall health of our nation at risk, but so too is our position as the global leader in biomedical research and innovation. Unfortunately, the United States is reducing its investments in biomedical research at a time when nations such as the United Kingdom, Singapore, and China are significantly increasing theirs. For example, China has pledged to invest more than \$300 billion in biomedical research over the next five years (182). If current trends continue, in only a few years, Chinese investment in life sciences research will be double that of the United States. To continue to make progress against cancer and maintain our global leadership in biomedical research, the United States must recruit, nurture, and retain a highly skilled and diverse cancer research workforce. The decline in NIH funding for biomedical research jeopardizes our ability to accomplish this.

At a time of constrained budgets, scarce federal dollars must be invested wisely. Funding cancer research and biomedical science through the NIH and NCI is a wise choice that will improve America's health and prosperity. Supporting these agencies must remain a national priority.

### Life Under Sequestration

As a result of the Budget Control Act of 2011 and Congress' failure to come to an agreement on long-term deficit reduction, across-the-board cuts known as sequestration went into effect March 1, 2013. The cut to the National Institutes of Health (NIH) was 5.1 percent, or \$1.6 billion, and the cut to the National Cancer Institute (NCI), the largest NIH institute, was \$293 million. Following the cut and the completion of the fiscal year (FY) 2013 appropriations bills, the budget for the NIH stands at approximately \$29 billion, the lowest funding level in terms of actual dollars in more than five years.

A cut of this magnitude has, according to NIH Director Francis Collins, M.D., Ph.D., adversely affected every aspect of the agency's work and is posing particular difficulties for scientists who are trying to start their careers in research.

#### Consider the numbers: NIH

FY 2012 funding level	<b>\$30.6 billion</b>
2013 across-the-board budget cut (5.1 percent)	<b>\$1.6 billion</b>
Current FY 2013 funding level	<b>\$29 billion</b>
Loss of competing grants	<b>703</b>
Total grants lost	<b>1,357</b>
Potential U.S. job losses	<b>20,000</b>
Expected lost economic activity	<b>\$3 billion</b>

For information on the current status of NIH funding, go to <http://cancerprogressreport.org/Pages/FederalFunding.aspx>

## The AACR Call to Action

To fulfill the extraordinary scientific and medical promise of cancer research and biomedical science, **the AACR respectfully urges Congress to:**

- **designate the NIH and NCI as national priorities** by providing annual budget increases at least comparable to the biomedical inflation rate; and
- **protect the NIH and NCI** from another year of the insidious cuts from sequestration, and **reinstate the \$1.6 billion** in funding that the NIH lost in March 2013.

Therefore, the AACR calls on all members of Congress to ensure that funding for cancer research and biomedical science is strongly supported. **The AACR also urges all Americans** — the beneficiaries of this lifesaving research — to **make their voices heard** by encouraging their policymakers to provide sustainable funding increases for the NIH.

If we are to **ultimately transform scientific discoveries into therapies** that improve and save the lives of cancer patients, it is going to require an **unwavering commitment** of Congress and the administration to invest in our country's **remarkably productive** cancer research and biomedical research enterprise led by the NIH and NCI.

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# Glossary A-E

**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 lymphocytic leukemia.

**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.

**BCR-ABL** - A protein made from pieces of two genes that are joined together. It is found in most patients with chronic myelogenous leukemia (CML), and in some patients with acute lymphocytic leukemia (ALL) or acute myelogenous leukemia (AML). Inside the leukemia cells, the ABL gene from chromosome 9 joins to the BCR gene on chromosome 22 to form the BCR-ABL fusion gene, which makes the BCR-ABL fusion protein.

**Biomedical Research Inflation** - Biomedical research 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. Over the past five years, the biomedical inflation rate has been double the economy-wide inflation rate on average.

**Biospecimen** - Samples of material, such as urine, blood, tissue, cells, DNA, RNA, and protein from humans, animals, or plants. Biospecimens are stored in a biobank or biorepository and are used for laboratory research. If the samples are from people, medical information may also be stored along with a written consent to use the samples in laboratory studies.

**Biomarker** - A biological molecule found in blood, 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.

**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.

**Breast cancer resistance genes 1 and 2 (BRCA1/2)** - Genes that normally help to suppress cell growth. A person who inherits certain mutations (changes) in a BRCA1 or BRCA2 gene has a higher risk of getting breast, ovarian, prostate, and some other types of cancer.

**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. Carcinoma is a cancer that begins in the skin or in tissues that line or cover internal organs. Sarcoma is a cancer that begins in bone, cartilage, fat, muscle, blood vessels, or other connective or supportive tissue. Leukemia is a cancer that starts in blood-forming tissue such as the bone marrow, and causes large numbers of abnormal blood cells to be produced and enter the blood. Lymphoma and multiple myeloma are cancers that begin in the cells of the immune system. Central nervous system cancers are cancers that begin in the tissues of the brain and spinal cord. Also called malignancy.

**Carcinogen** - Any substance that causes cancer.

**Cervical cancer** - 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 papilloma virus (HPV). Normal cells of the cervix do not suddenly become cancerous, they first gradually develop precancerous changes then later turn into cancer. These changes can be detected by the 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 myelogenous leukemia (CML)** - A slowly progressing disease in which too many white blood cells (not lymphocytes) are made in the bone marrow. Also called chronic granulocytic leukemia and chronic myeloid leukemia.

**Clinical trial** - A type of research study that tests how well new medical approaches work in people. These studies test new methods of screening, prevention, diagnosis, or treatment of a disease. Also called clinical study.

**Clinical trial phase** - A part of the clinical research process that answers specific questions about whether treatments that are being studied work and are safe. Phase I trials test the best way to give a new treatment and the best safe dose. Phase II trials test whether a new treatment has an effect on the disease. Phase III trials compare the results of people taking a new treatment with the results of people taking the standard treatment. Phase IV trials are done using large populations of people after a treatment has been approved and marketed, to check for side effects that were not seen in the phase III trial.

**Colonoscopy** - Examination of the inside of the colon using a colonoscope, 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% of colorectal cancers are adenocarcinomas that start in cells that form 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 have the chance to turn into cancer.

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

**Cytotoxic chemotherapy** - Anticancer drugs that kill cells, especially 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, live in one area of the country, or who are of a certain gender, age, or ethnic group.

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

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

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

**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.

**Epidemiology** - The study of the patterns, causes, and control of disease in groups of people.

# Glossary E-P

**Epigenetics** - The study of heritable changes in gene expression or cellular phenotype caused by mechanisms other than changes in the underlying 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.

**Gastrointestinal stromal tumor (GIST)** - A type of tumor that usually begins in cells in the wall of the gastrointestinal tract. It can be benign or malignant.

**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.

**Growth factor** - A substance made by the body that functions to regulate cell division and cell survival. Some growth factors can be produced in the laboratory and used in biological therapy.

**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 may also play a role in some other types of cancer, such as anal, vaginal, vulvar, penile, oropharyngeal, and squamous cell skin cancers.

**Inflammation** - Redness, swelling, pain and/or a feeling of heat in an area of the body. This is a protective reaction to injury, disease, or irritation of the tissues.

**Inflammatory breast cancer** - A rare and very aggressive disease in which cancer cells block lymphatic vessels (see **Lymphatic vessels**) in the skin of the breast. This type of breast cancer is called "inflammatory" because the breast often looks swollen and red, or "inflamed." Inflammatory breast cancer accounts for 1 to 5 percent of all breast cancers diagnosed in the United States.

**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, 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, functioning to maintain fluid balance. 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, like blood vessels, into all the tissues of the body.

**Magnetic resonance cholangiopancreatography (MRCP)** - A medical imaging technique that uses magnetic resonance imaging to visualize the biliary and pancreatic ducts in a noninvasive manner.

**Mammalian target of rapamycin (mTOR)** - A protein kinase that regulates cell growth, cell proliferation, cell motility, cell survival, protein synthesis, and transcription. mTOR is also known as mechanistic target of rapamycin or FK506 binding protein 12-rapamycin associated protein 1 (FRAP1).

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

**Mastectomy** - Surgery to remove the breast (or as much of the breast tissue as possible).

**Melanoma** - A form of cancer that begins in melanocytes (cells that make the pigment melanin). It may begin in a mole (skin melanoma), but it can also begin in other pigmented tissues, such as in the eye or in the intestines.

**Metastasis** - The spread of cancer from one part of the body to another. A tumor formed by cells that have spread is called a "metastatic tumor" or a "metastasis." The metastatic tumor contains cells that are like those in the original (primary) tumor. The plural form of metastasis is metastases.

**Multiple myeloma** - A type of cancer that begins in plasma cells (white blood cells that produce antibodies). Also called Kahler disease, myelomatosis, and plasma cell myeloma.

**Mutation** - Any change in the DNA of a cell. Mutations may be caused by mistakes during cell proliferation or by exposure to DNA-damaging agents in the environment. Mutations can be harmful, beneficial, or have no effect. If they occur in cells that make eggs or sperm, they can be inherited; if mutations occur in other types of cells, they are not inherited. Certain mutations may lead to cancer or other diseases.

**Nanotechnology** - A technology executed on the scale of less than 100 nanometers, the goal of which is to control individual atoms and molecules, especially to create computer chips and other microscopic devices.

**Non-small cell lung carcinoma** - 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 gene that is 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 caused by being exposed to substances in the environment that cause cancer.

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

**Papanicolaou (Pap) test** - A test of a sample of cells taken from a woman's cervix. The test is used to look for changes in the cells of the cervix that show 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.

# Glossary P-V

**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 in the pancreas that make the “juice” that helps digest food, and the most common of these cancers are called adenocarcinomas. Pancreatic cancers that arise in the cells of the pancreas that help control blood sugar levels are called pancreatic neuroendocrine tumors.

**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.

**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.

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

**Prostatic Specific Antigen (PSA)** - A protein secreted by the prostate gland, increased levels of which are found in the blood of patients with cancer of the prostate.

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

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

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

**Receptor** - A protein in a cell that attaches to specific molecules, 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.

**Renal cell carcinoma** - The most common type of kidney cancer. It begins in the lining of the renal tubules in the kidney. The renal tubules filter the blood and produce urine. Also called hypernephroma, renal cell adenocarcinoma, and renal cell cancer.

**Signaling pathway/signaling network** - A group of molecules in a cell that work together to control one or more cell functions, such as cell proliferation or cell death. After the first molecule in a pathway receives a signal, it 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. This may help block 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 biomarker (see **Biomarker**) intended to substitute for a clinical endpoint (see **Endpoint**). Surrogate markers are 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. The U.S. Food and Drug Administration and other regulatory agencies will often accept evidence from clinical trials that show a direct clinical benefit to surrogate markers.

**T cell** - A type of immune cell that protects the body from invading microorganisms and other foreign substances, and 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 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 that helps control cell growth. Mutations (changes in DNA) in tumor suppressor genes may lead to cancer. Also called antioncogene.

**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.

**Vascular endothelial growth factor (VEGF)** - A family of signaling proteins that bind to molecules called VEGF receptors, found mostly on the surface of cells lining blood and lymphatic vessel walls, causing an increase in the number or branches of blood and lymphatic vessels.

**Table1A: 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	gemcitabine	Gemzar
Certain leukemias	hydroxyurea	Droxia
Multiple cancers	methotrexate	Rheumatrex; Trexall
Multiple cancers	mitomycin	Mutamycin
Certain leukemias; lymphoma	nelarabine	Arranon
Lung and ovarian cancers; mesothelioma	pemetrexed	Alimta
Certain leukemias	pentostatin	Nipent
Certain lymphomas	pralatrexate	Folotyn
DNA Damaging Agents		
Approved Indication	Generic Name	Trade Name
Ovarian cancer	altretamine	Hexalen
Certain leukemias	arsenic trioxide	Trisenox
Multiple cancers	bendamustine	Treanda
Certain lymphomas; squamous cell and testicular cancers	bleomycin sulfate	Blenoxane
Certain leukemias	busulfan	Myleran; Busulfex
Breast, lung and ovarian cancers	carboplatin	Paraplatin; Paraplat
Brain tumors; certain lymphomas	carmustine	BiCNU
Multiple cancers	chlorambucil	Leukeran
Multiple cancers	cisplatin	Platinol-AQ
Multiple cancers	cyclophosphamide	Cytoxan
Melanoma; certain brain cancers	dacarbazine	DTIC-Dome
Multiple cancers	dactinomycin	Cosmegen
Certain leukemias	daunorubicin; daunomycin	Cerubidine
Multiple cancers	doxorubicin hydrochloride	Adriamycin PFS; Adriamycin RDF
Certain leukemias; breast and stomach cancers	epirubicin hydrochloride	Ellence
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	melfhalan	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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**Table1A: FDA-approved Chemicals for the Treatment of Cancer (cont.)**

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
<b>Immune System Modifiers</b>		
<b>Approved Indication</b>	<b>Generic Name</b>	<b>Trade Name</b>
Multiple cancers	interferon alfa-2b	Intron A
Melanoma; kidney cancer	aldesleukin	Proleukin
Myelodysplastic syndrome; certain lymphomas	lenalidomide	Revlimid
Multiple myeloma	pomalidomide	Pomalyst
<b>Proteasome Inhibitor</b>		
<b>Approved Indication</b>	<b>Generic Name</b>	<b>Trade Name</b>
Multiple myeloma	bortezomib	Velcade
Multiple myeloma	carfilzomib	Kyprolis
<b>Protein Translation Inhibitor</b>		
<b>Approved Indication</b>	<b>Generic Name</b>	<b>Trade Name</b>
Certain type of leukemia	Omacetaxine mepesuccinate	Synribo
<b>Epigenetic Modifiers</b>		
<b>Approved Indication</b>	<b>Generic Name</b>	<b>Trade Name</b>
Myelodysplastic syndrome	azacitidine	Vidaza
Myelodysplastic syndrome	decitabine	Dacogen
Certain lymphomas	romidepsin	Istodax
Certain lymphomas	vorinostat	Zolinza
<b>Angiogenesis Inhibitors</b>		
<b>Approved Indication</b>	<b>Generic Name</b>	<b>Trade Name</b>
Kidney cancer	axitinib	Inlyta
Thyroid cancer	cabozantinib	Cometriq
Kidney cancer; soft tissue sarcomas; gastrointestinal stromal tumors	pazopanib	Votrient
Colorectal cancer; gastrointestinal stromal tumors	Regorafenib	Stivarga
Kidney cancer	sorafenib	Nexavar
Gastrointestinal stromal tumors; kidney cancer; some pancreatic cancers	sunitinib	Sutent
Thyroid cancer	vandetanib	Caprelsa
<b>Cell Signaling Inhibitors</b>		
<b>Approved Indication</b>	<b>Generic Name</b>	<b>Trade Name</b>
Certain type of lung cancer	afatinib	Gilotrif
Certain type of leukemia	bosutinib	Bosulif

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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
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

\* includes companion diagnostic

\*\* mechanism is not completely clear

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

**Table 1B: FDA-approved Monoclonal Antibodies for Oncology**

Angiogenesis Inhibitor		
Approved Indication	Generic Name	Trade Name
Colon; kidney; and lung cancers	bevacizumab	Avastin
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 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	Erbix
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

**Table 2A: 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	Pancreatoduodenectomy
Rectal cancer	Total mesorectal excision
Prostate cancer	Nerve-sparing prostatectomy
Rectal cancer	Transanal Endoscopic Microsurgery (TEM)
Testicular cancer	Modified retroperitoneal lymph node dissection
Breast, melanoma, and colorectal cancers	Sentinel lymph node biopsies
Breast cancer, laryngeal cancer, and anal/rectal cancer	Neoadjuvant chemotherapy
Multiple cancers	Robotic or computer-assisted surgeries
Radiotherapy 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

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