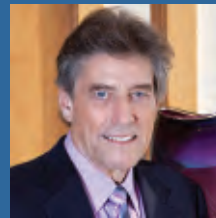
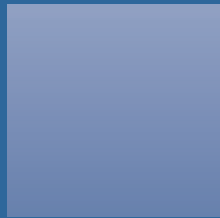
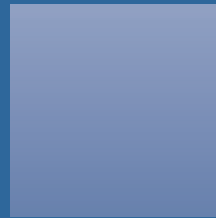
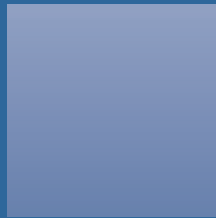
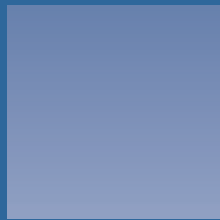
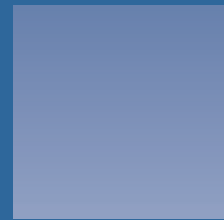
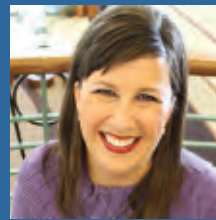
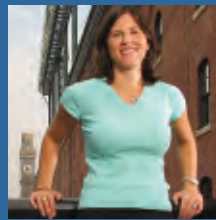
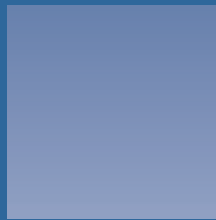
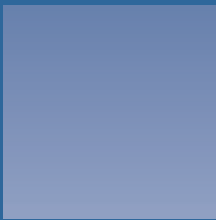
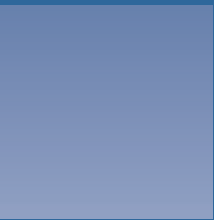


# AACR Cancer **Progress** Report **2012**

*Making Research Count for Patients: A New Day*



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

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AACR Cancer **Progress** Report  
**2012**

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

*Making Research Count for Patients: A New Day*



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# Cancer Progress Report

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# A Message from the AACR



*McCormick*



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*Foti*

At the opening of its Annual Meeting on April 1, 2012, in Chicago, Illinois, leaders from the American Association for Cancer Research (AACR) declared that the ability of cancer researchers to bring the promise of science to improve the outcomes for cancer patients is in peril due to a decade of declining budgets at the National Institutes of Health (NIH) and the National Cancer Institute (NCI). The AACR Board of Directors also announced that it would redouble its efforts to engage with Congress to make cancer research and biomedical science funding a national priority, raise public awareness of the importance of continued investment in cancer research and biomedical science, and call on its 34,000 members and the broader advocacy community constituencies to join together to better explain the value of research to saving lives and to the economic health and well-being of our Nation.

The AACR Cancer Progress Report 2012 is one of the major steps toward achieving the goals outlined five months ago by the AACR Board. In addition to detailing how scientific discoveries are transforming the prevention, detection, diagnosis and treatment of cancer and ushering in a new era of personalized medicine where cancer patients are treated based on the molecular profile of their cancer, this Report is a Call to Action for the general public and for policymakers to intensify their efforts to support research. The AACR is deeply grateful to the cancer survivors and their loved ones who selflessly shared in this Report their personal experiences to further our efforts to communicate the importance of research to each and every individual facing cancer.

For the past decade the NIH budget has remained essentially flat, and when factoring in the rate of biomedical inflation, the agency has effectively lost more than \$6 billion or nearly 20% of its ability to support life-saving research. And as a result of a budget mechanism, called sequestration, which was created by the U.S. Congress in the Budget Control Act of 2011 to force the government to address the federal deficit, on January 2, 2013, funding for every federal program, including the NCI and its parent agency, the NIH, may be forced to absorb another budget cut of 8%.



*Hawk*



*Laird*



*Pivnicka-Worms*

If these cuts are put in place, it will destroy the cancer research and biomedical science enterprise, which is already confronting a situation where the opportunities for researchers to be awarded an NIH grant to uncover new scientific knowledge and make further substantial inroads against cancer have reached an all-time low. In testimony before Congress, NIH Director Francis Collins, M.D., Ph.D., described sequestration's impact on NIH as potentially "devastating," and explained that NIH would be forced to fund 2,300 fewer grants than planned in fiscal year 2013. This scenario would be disastrous for our most precious national resource, the young investigators who are just beginning their professional careers in research with an eye toward making a difference. We are relying on these young investigators to continue to nourish the pipeline of new discoveries that will have an even greater impact on the welfare of patients and on public health as a whole.

As detailed throughout the Report, these funding constraints are coming at a time when the number of opportunities for exploiting our growing scientific knowledge against cancer has never been greater. The myriad advances in cancer research and biomedical science bring a sense of hope to all who face cancer or who love someone facing cancer, as poignantly illustrated by the personal stories shared in this Report. Clearly, as we observe the increasing incidence and mortality due to cancer not only in the U.S., but also around the world, we believe that our great Nation has a responsibility to step up to the plate and make a commitment to eradicating this devastating disease at the earliest possible time.

Sequestration can be prevented if Congress enacts legislation this year that provides alternative means to reduce the federal

government's budget deficit. Therefore, we are urging all AACR members and the broader advocacy community to contact their representatives and senators in Congress to urge them to work in a constructive, bipartisan fashion to find a more balanced approach to address the federal deficit and prevent sequestration from occurring. We cannot compromise our ability to transform cancer care for the benefit of current and future cancer patients, for by doing so we risk losing the momentum we have already achieved in cancer science and medicine.

With the availability of new technological tools, cancer researchers are now able to find new and efficient ways to decipher the complexities of cancer. As a result, breakthroughs against human cancer are being discovered at an ever-increasing pace. Cancer survivors are coming together to speak with one voice about the urgency of finding new cures for patients today and for future generations. And Members of Congress have no other option but to recognize that they have the responsibility to invest in the health of our citizens.

By all of us working together – scientists, survivors and patient advocates, citizen activists, and legislators – we will accelerate further progress and we will defeat cancer.

**Frank McCormick, Ph.D., FRS, D.Sc. (hon.)**  
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## About the American Association for Cancer Research

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 the advances in 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 nearly 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 seven major peer-reviewed journals: *Cancer Discovery*; *Cancer Research*; *Clinical Cancer Research*; *Molecular Cancer Therapeutics*; *Molecular Cancer Research*; *Cancer Epidemiology, Biomarkers & Prevention*; and *Cancer Prevention Research*. In 2011, 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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# An Appeal from Cancer Survivors and Their Loved Ones to Make Research a National Priority

No one who faces a diagnosis of cancer is ever fully prepared for the challenges that confront them and their loved ones. Hearing the words “you’ve got cancer” changes life, forever. Cancer remains in the forefront of our minds whether we are currently in treatment, living well beyond its diagnosis or coping with the loss of a loved one.

Cancer can strike anyone—no age, gender, race, ethnicity, socioeconomic status or political affiliation makes you immune. In fact, in the United States, one out of every three women and one out of every two men will receive a cancer diagnosis in their lifetimes.

As cancer survivors and advocates, we, like millions of others, battle this terrifying disease on a personal level through our own individual experiences. But it is also critical that everyone touched by cancer come together to advocate on a national level for the needs of those currently facing cancer and those who will face it in the future. Our drive to make a difference is why we wanted to be part of the AACR Cancer Progress Report 2012, to share our personal stories and put a face on the difference that cancer research has made *and still needs to make*.

To be honest, for many of us before we received a diagnosis of cancer, the National Cancer Institute (NCI) and its parent agency, the National Institutes of Health (NIH), were either unknown or seen as agencies that supported abstract research that was not terribly connected to our daily lives. Now, we understand and appreciate that, far from being abstract, these agencies serve a critical and irreplaceable role in stimulating scientific breakthroughs, which are the foundations for the medical treatments we all rely on today and which hold the promise for new cures and prolonged quality of life. Advances accrued over the past decades of cancer research supported by these agencies have fundamentally changed the conversations that Americans are having today about cancer.

From across the diversity of our cancer diagnoses, we are united in our belief that our greatest source of hope for healthier and longer lives for current cancer survivors and future generations is grounded in scientific discovery.

Sadly, despite the remarkable progress that has been made against cancer over the past four decades, a grim reality remains.

Too many Americans are losing their battle with this disease that we now know is a collection of more than 200 different types of cancer. More than 1.64 million Americans will be diagnosed in 2012, and more than 570,000 will succumb to this disease. No matter which form of cancer has stricken us, we all know too well the horrific toll of a cancer diagnosis, the fear of what tomorrow might bring, and the pain and confusion that can follow is indescribable.

With a burden so high, it is unbelievable to us that support for cancer research and biomedical science seems to be waning. The budgets of the NCI and the NIH have been falling over the past decade and are down in functional dollars by about 20%. We fear that the once determined resolve of our Nation to find a cure for cancer has eroded alongside these deteriorating budgets. We are extremely concerned that our nation’s policymakers will not act to avert sequestration, which would make deep cuts to these programs, causing profound and catastrophic harm to the future of biomedical research in this country. These potential cuts threaten to compromise the progress we have made and destroy the hope for every one of us whose future depends on the breakthrough scientific discoveries that could lead to new and more effective treatments.

Our message is simple but earnest. Congress, help us continue the momentum necessary to combat the cancer epidemic, and make funding for cancer research and biomedical science a priority. There is no time to waste when, in the U.S. alone, we are losing one person every minute of every day to this devastating disease.

Signed:

Monica Barlow  
Kathryn Becker  
Congressman M. Robert Carr  
S. Ward “Trip” Casscells, M.D.  
Shaundra L. Hall  
Wendy and Gavin Lindberg, Parents of Evan Lindberg  
Amy Mulford, Mother of Brooke Mulford  
Melanie A. Nix  
Lori Redmer  
Antoni Smith  
Jill Ward







# Executive Summary

## Background

Cancer research saves lives, fueling the development of new and better ways to prevent, detect, diagnose and treat cancer in all age groups. The AACR Cancer Progress Report 2012 celebrates the many ways that we have made research count for cancer patients, highlighting important advances seen in the past year. Decades of prior research have provided the foundation for the progress that is helping to usher in a new day for patients with many forms of cancer. Indeed, scientific progress has spurred improvements in health care that have significantly reduced the burden of cancer and transformed the lives of a growing number of the 13.7 million cancer survivors in the U.S. and their families and other loved ones. These advances would not have been possible without the long-standing, bipartisan commitment of our Nation's policymakers to invest in research through the National Institutes of Health (NIH) and National Cancer Institute (NCI), the foundation of our Nation's biomedical research enterprise.

An estimated 577,000 Americans will die from cancer in 2012, despite these remarkable advances. Moreover, because cancer is predominantly a disease of aging, we face a future where the number of cancer deaths will increase dramatically. In fact, as an increasing proportion of the population is over the age of 65, cancer is predicted to soon become the number one killer of Americans, a trend that will also occur globally. Cancer is already the most costly disease to the Nation, and without major new research advances to facilitate the successful development of new preventive interventions and treatments, these trends will magnify the already huge economic burden that cancer manifests.

The dedicated work of thousands of cancer and biomedical researchers the world over has uncovered much about the complexities of cancer—we now know that cancer is, in fact, not a single disease, but 200 different diseases. This diversity exists at every level, from populations to the very genetic and molecular abnormalities that drive a patient's cancer. Although the complex, diverse nature of cancer is daunting, we have discovered that some common biological processes are involved in cancer. We have learned that changes in an individual's genes alter specific components of the molecular machinery of a cell to drive cancer initiation, development and spread (metastasis), and that therapies specifically targeting these defects are often beneficial to the patients while having less toxicity than older therapies.

With this new knowledge, we have never been better positioned to capitalize on our hard-won understanding of cancer—what causes it, what drives it—and there is enormous optimism that we can achieve our ultimate goal of defeating cancer. Unfortunately, continued progress in life-saving cancer research is in jeopardy, as investments in the NIH and NCI have been steadily declining since 2003. We are now facing the acute consequences of automatic budget-cutting sequestration, which will begin on Jan. 2, 2013, if Congress fails to find a more balanced approach to address the federal deficit.

This second AACR Cancer Progress Report to Congress and the American public seeks to again serve as a comprehensive educational tool that illustrates the astounding return on investment in cancer research and biomedical science supported by the NIH and NCI, while also specifically capturing the major advances that occurred in just 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 commitment on the part of Congress and the Administration to invest in our country's remarkably productive biomedical research enterprise led by the NIH and NCI.

## Prevention and Early Detection

One of the key areas of progress and promise is cancer prevention. As a direct result of our scientific understanding of the timing, sequence and frequency of the pivotal changes underlying cancer development and spread throughout the body, we now know there are points of intervention that can be exploited in order to stop certain cancers in their tracks, before they do irreversible damage that results in death. In fact, advances in cancer prevention and early detection have resulted in some of the greatest reductions in cancer mortality in recent decades. Implementing public health measures to reduce exposure to cancer-causing agents, intervening medically to treat or prevent infectious causes of cancer and introducing population-based screening practices have contributed to this progress.

Unfortunately, it is estimated that about two out of every three cancer deaths in the U.S. in 2012 will be due to preventable

causes—most notably tobacco use, obesity and physical inactivity and failure to use or comply with interventions that treat or prevent infectious causes of cancer. These facts underscore the need for continued research to inform effective public educational campaigns and programs that can encourage and help people change their behaviors.

Population-based screening programs have been credited with dramatically increasing the five-year survival rates for the cancers that they detect because finding a tumor early makes it more likely that it can be treated successfully and with fewer side effects. There is concern, however, that this heightened surveillance can lead to overdiagnosis and overtreatment, potentially causing more harm than good. More research to address these problems is vital to ensure that the public has confidence in current screening guidelines and in any future recommendations that may be made. In addition, we need to develop screening strategies for those cancers that we cannot detect early, in particular, those that currently elude detection until they are at an advanced stage.

## Making Research Count for Patients

Decades of research have provided an understanding of the fundamental nature of cancer, and why and how cancer develops and spreads throughout the body. These major discoveries about the biology of cancer are beginning to be translated into new breakthrough therapies that are being used alongside the traditional triad of cancer patient care—surgery, radiotherapy and chemotherapy—to transform the treatment of patients with certain forms of cancer. In the past 12 months alone (September 2011 through the end of August 2012), the Food and Drug Administration (FDA) U.S. approved eight new drugs for the treatment of cancer as well as new uses for three previously approved drugs, increasing the number of patients benefiting from these therapies. There are also numerous ongoing clinical trials testing other agents, several of which are showing promise for near-term clinical advances.

The majority of the cancer therapies approved by the FDA in the past 12 months are more effective and less toxic than older treatments that have been the mainstay of patient care. As a result, these new therapies are not only saving the lives of countless cancer patients, but are also improving their quality of life. Rapid

advances in this area are likely in the near future, as we learn more about patient characteristics that predict their response to a certain therapy. Patients identified as likely to respond will receive treatment, while those determined to be very unlikely to respond will be spared any adverse side effects from the course of therapy. Moreover, definitive stratification of patient populations can also provide healthcare savings by avoiding the futile use of ineffective courses of cancer treatments and the treatment costs associated with their adverse effects.

Unfortunately, progress has not been uniform for all forms of cancer, and this highlights the great need for continued cancer research. Large-scale analyses of the genetic underpinnings of cancer are now guiding the development of new cancer drugs and are directing the repurposing of proven therapies to treat novel cancer types. Further innovation is needed, however, if genetic/genomic analysis is to become part of standard 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.

While the altered genomes of cancer cells can have a profound effect on the development and spread of cancer, factors at all levels—from molecules to cells to humans—are involved. Understanding all of these influences will help to determine which can be exploited to most significantly impact patient care. In addition, it is vital that we learn not only how these factors work in isolation, but also how they affect each other. While progress is beginning to be made in several areas, it will take a concerted effort from all in the cancer research community to deliver future breakthroughs.

## What is Required for Continued Progress Against Cancer?

Congressional support for the NIH and NCI has enabled extraordinary progress against cancer, and in doing so has saved countless lives while catalyzing the development of the biotechnology industry and economic growth in America. The research-fueled explosion of both knowledge and technological innovation, as well as our ever-increasing understanding of how to apply this new information, has provided new ways to reduce the



Globally, in 2008 an estimated **12.7 million** people were diagnosed with cancer and **7.6 million** died of the disease. By 2030, it is estimated that this will increase to **22.2 million** and **13.2 million**, respectively.

global burden of cancer. However, there are many challenges to overcome if we are to realize our goal of defeating cancer.

If we are to make a quantum leap in our progress against all cancers, we must continue to pursue a comprehensive understanding of cancer. With new tools, new analytics, new ways of thinking and new ways of working together, we will gather speed in furthering our knowledge base and develop new approaches to cancer prevention, detection, diagnosis and treatment.

We live in a time of unprecedented scientific opportunities, afforded to us by past investments in cancer research and biomedical science. Researchers and their partners in the cancer research community possess the steadfast resolve to seize the day and forge ahead to the finish line—to the day when cancer is removed a major threat to our Nation’s citizens and to future generations. Realizing this bright future requires that Congress and the general public stand firm in their commitment to the conquest of cancer. At a time when budgets are constrained and there is the looming threat of sequestration, scarce federal dollars must be invested wisely. Funding cancer research and biomedical science through the NIH and NCI is a wise choice for our Nation’s future.

## The AACR Call to Action

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

- Work in a constructive, bipartisan fashion to find a more balanced approach to address the federal deficit and prevent sequestration from occurring on Jan. 2, 2013; and
- Designate NIH and NCI as a top national priority by providing annual budget increases at least comparable to the biomedical inflation rate.

While it is imperative that Congress take action to stop the threatened sequestration and once again make NIH and NCI funding a national priority, the responsibility is not theirs alone. The AACR also urges the citizens of this great Nation, who benefit from this life-saving research, to urge their legislators to support cancer research and biomedical science.

In short, if we are to ultimately transform scientific discoveries into therapies that improve the lives of cancer patients, an unwavering commitment on the part of Congress and the Administration to invest in our country’s biomedical research enterprise is urgently needed.

“Thousands of Americans lose their battle to cancer each year. But through the committed efforts of scientists and hospitals around the country, great strides are being made to discover cures and treatments to change this sad reality. By raising awareness about early detection and prevention as well as prioritizing research to treat and cure cancer, I am confident we will one day win this fight.”

**Senator Kay Bailey Hutchison (R-TX)**

**Co-Chair of the Senate Cancer Coalition**



# A Snapshot of a Year of Progress

It is a new day for cancer research and for cancer patients. Rapidly evolving technology is enabling extraordinary advances in cancer research that deepen our understanding of how cancer develops, grows and threatens the lives of millions. By exploiting this growing body of knowledge about cancer biology, we can be more strategic and innovative than ever before in the way we attack cancer. This is quickening the pace of developing new ways to prevent, detect, diagnose and treat cancer.

The AACR Cancer Progress Report 2012 celebrates the many ways that we have made research count for cancer patients, particularly in the past year alone. Decades of research, in large part thanks to our Nation's long-standing investment in cancer research and biomedical science by the National Institutes of Health (NIH) and the National Cancer Institute (NCI), have provided the foundation for the progress that is helping usher in this new day for patients with many forms of cancer.

Highlighted in this Report are treatment advances approved by the U.S. Food and Drug Administration (FDA) in the past 12 months alone:

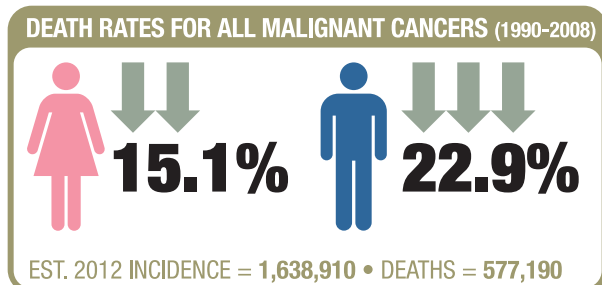
- A new drug for treating precancerous lesions of the skin
- Eight new drugs for treating a variety of types of cancer, of which two are entirely new classes of drugs
- Four new uses for previously approved cancer drugs, one of the four uses being an alternative administration to reduce side effects

There are many cancer therapeutics showing tremendous potential in clinical trials. Some of these are currently being reviewed by the FDA and could provide widespread patient benefit in the near term; others require further study in larger populations before they can be considered by the FDA. Several promising cancer treatments are discussed herein, but this Report should not be considered an exhaustive summary of potential areas of future progress.

The Report also presents new discoveries that are forming the foundation of tomorrow's progress. Scientists at institutions in every state across the Nation continue to report a myriad of basic science breakthroughs that are revealing novel insights that may well offer the key to the next major advances.

Unfortunately, continued progress against cancer is in jeopardy due to the current crisis in funding for cancer research and biomedical science at the federal level. Without action to avert further cuts, our Nation's ability to seize today's scientific momentum and capitalize on prior investments in cancer research, spur innovation, and most importantly, save lives is at risk. Because of a decade of essentially flat budgets, compounded further by biomedical inflation, the NIH and NCI have effectively lost \$6 billion or nearly 20% of its ability to support life-saving research. Sequestration, with its automatic budget cuts, threatens to set these agencies back to budget levels last seen in 2004.

As a reminder of why it is so critical for the Nation to prioritize cancer research and biomedical science, the 2012 Report describes the exciting research progress and scientific opportunities ahead. Also, to put a face on the realities of cancer, we have chronicled the experiences and the sentiments of twelve cancer survivors, and as well as a mother and father who suffered unimaginable grief when their seven-year-old child died of neuroblastoma.





# The Status of Cancer in 2012

**Table 1: Newly FDA-Approved Drugs and Indications for the Treatment of Cancer and Precancerous Lesions - September 2011 to August 2012**

Angiogenesis Inhibitors		
Approved Indication	Generic Name	Trade Name
Kidney cancer	axitinib	Inlyta
Soft tissue sarcomas*	pazopanib	Votrient
Colorectal cancer	ziv-aflibercept	Zaltrap
Cell Cytoskeleton Modifying Agents		
Approved Indication	Generic Name	Trade Name
Certain leukemias and lymphomas	vincristine sulfate liposomes	Marqibo
Cell Signaling Inhibitors		
Approved Indication	Generic Name	Trade Name
Non-cancerous kidney tumors*; HER2+ breast cancers*	everolimus	Afinitor
HER2+ breast cancers	pertuzumab	Perjeta
Myelofibrosis	ruxolitinib	Jakafi
Certain type of skin cancer	vismodegib	Erivedge
Hormone/Antihormone		
Approved Indication	Generic Name	Trade Name
Prostate cancer	enzalutamide	Xtandi
Immune System Modifiers		
Approved Indication	Generic Name	Trade Name
Precancerous skin lesions	ingenol mebutate	Picato
Proteasome Inhibitor		
Approved Indication	Generic Name	Trade Name
Multiple myeloma	bortezomib**	Velcade
Multiple myeloma	carfilzomib	Kyprolis

\* New indication for 2012.

\*\* New route of administration for 2012.

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

The number of cancer survivors in the United States (U.S.) continues to increase year after year, from 3 million in 1971, the year the U.S. Congress passed the National Cancer Act, to approximately 13.7 million in 2012 (1, 2). This success is the result of several factors – the investments in research by the federal government as well as philanthropic individuals and the private sector, and behavioral changes, especially the reduction of tobacco consumption. The decades of investments in basic and clinical cancer research and biomedical science, in particular the investments supported by public funds through the National Institutes of Health (NIH) and the National Cancer Institute (NCI), have spurred the development of new and better ways to prevent, detect, diagnose and treat cancer in all age groups, leading to decreases in incidence; cures for some patients with certain types of cancer; and higher quality, longer lives for many of those individuals whose cancers cannot yet be prevented or cured.



- Is **27** institutes and centers
- funds nearly **6,000** in-house scientists and **50,000** annual external grants
- enables the work of over **432,000** extramural researchers at over **3,000** universities, medical schools, medical centers, teaching hospitals, small businesses and research institutions
- **creates jobs in every state and around the world.**

Now, more than any other time in our history, cancer researchers are maximizing the impact of the fundamental discoveries made during the past four-plus decades and are translating them into improved patient care. In the past 12 months alone (September 2011 through August 2012), the Food and Drug Administration (FDA) approved one new drug for treating precancerous lesions, nine new drugs for treating cancers and three new uses for previously approved drugs (see **Table 1**).

However, the vast complexity of cancer, which is in fact not one disease but more than 200 different diseases, has meant that advances have not been uniform for all forms of cancer (see **Table 2** p. 15). The good news is that the five-year survival rate for

**Table 2: Select Cancer Incidence, Mortality and Change in Death Rates (1990-2008)**

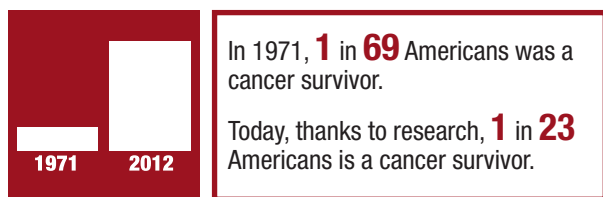
Cancer	Total est 2012 Incidence*	Total est 2012 deaths*	Change in Death Rates 1990-2008			
			Female	Male		
All Malignant Cancers	1,638,910	577,190	↓↓↓	-15.1	↓↓↓↓	-22.9
Oral Cavity & Pharynx	40,250	7,850	↓↓↓↓	-30.0	↓↓↓↓	-32.1
Esophagus	17,460	15,070	↓↓↓	-11.1	↑	5.6
Stomach	21,320	10,540	↓↓↓↓	-40.5	↓↓↓↓	-44.9
Colon and Rectum	143,460	51,690	↓↓↓↓	-33.0	↓↓↓↓	-36.0
Liver & Intrahepatic Bile Duct	28,720	20,550	↑↑↑↑	33.3	↑↑↑↑	58.5
Pancreas	43,920	37,390	↑	3.2	-	0.0
Larynx	12,360	3,650	-	0.0	↓↓↓	-30.0
Lung & Bronchus	226,160	160,340	↑	6.0	↓↓↓	-29.4
Melanoma of the skin	76,250	9,180	↓↓	-20.0	↑	7.9
Breast	229,060	39,920	↓↓↓	-32.0		
Cervix Uteri	12,710	4,220	↓↓↓↓	-35.1		
Corpus and Uterus, NOS	47,130	8,010	↓	-2.3		
Ovary	22,280	15,500	↓↓	-14.0		
Prostate	241,740	28,170			↓↓↓↓	-40.9
Urinary Bladder	73,510	14,880	↓	-8.3	↓	-5.0
Kidney & Renal Pelvis	64,770	13,570	↓	-10.7	↓	-6.5
Brain & Other Nervous System	22,910	13,700	↓↓	-12.5	↓	-11.7
Hodgkin Lymphoma	9,060	1,190	↓↓↓↓	-40.0	↓↓↓↓	-44.4
Non-Hodgkin Lymphoma	70,130	18,940	↓↓	-20.6	↓↓	-18.0
Myeloma	21,700	10,710	↓↓	-16.1	↓	-10.4
Leukemia	47,150	23,540	↓↓	-14.5	↓↓	-11.2



Underlying mortality data provided by NCHS ([www.cdc.gov/nchs](http://www.cdc.gov/nchs)).  
 Rates are per 100,000 and age-adjusted to the 2000 US Std Population (19 age groups - Census P25-1130) standard.  
 \*Both sexes.

all cancers is now about 65%. Significant progress has been made against some cancers, such as breast cancer. The five-year survival rate for female breast cancer patients is now 90% compared with 63% in the early 1960s (3). Another example is childhood acute lymphocytic leukemia, where the five-year survival rate is now greater than 90% versus 58% in the mid-1970s (3). In contrast, the five-year survival rates for other cancers, such as pancreatic, liver and lung cancers, remain very low at 6%, 14% and 16%, respectively (3). Moreover, the burden of cancer is not distributed evenly across the population, due to numerous interrelated factors (see **Sidebar on Cancer Health Disparities in America**, p. 16). These differences in survival rates underscore the great need for continued research in discovery, translation and dissemination science.

Despite significant improvements in survival from many cancers, it is estimated that more than 577,000 Americans will die from cancer in 2012. Cancer will account for nearly one of every four deaths, making it the second most common cause of death in the U.S. If current trends continue, it will not be long before cancer is the leading cause of death for Americans. It is therefore urgent that our Nation continues to invest in the scientific research necessary to develop effective preventive interventions and treatments.



More than 1.6 million Americans will be diagnosed with cancer in 2012 (3), and it is estimated that more than 41% of individuals born today will be diagnosed with cancer at some point during their lifetimes, which is nearly one out of every two Americans (4). The number of cancer diagnoses is likely to increase dramatically in the next few decades because cancer is predominantly a disease of aging. The majority of all cancer diagnoses are among those aged 65 years and older (4, 5), a rapidly expanding segment of the population (6, 7); see **Fig. 1**, p. 18). Compounding the problem is the growing prevalence of obesity and the continued practice of smoking, which are linked to an increased risk for several cancers (8). The combination of these trends will magnify the already huge economic burden of cancer.

The latest estimates from the NIH indicate that the overall economic cost of cancer in the U.S. in 2007 was \$226.8 billion (3),

# Cancer Health Disparities in America

While great strides have been made in cancer prevention and treatment, certain groups experience noticeably higher incidence of certain cancers than the general population and/or suffer significantly poorer treatment outcomes. A disproportionately higher burden of cancer falls on racial and ethnic minorities, as well as low-income and elderly populations. The causes of these disparities are numerous, complex, often interrelated and only partially understood. Chief among them are unequal access to quality health services; different behavioral, environmental and genetic risk factors; a lack of minority and elderly inclusion in the development of new therapies; and social and cultural biases that can negatively alter the relationship between patients and healthcare providers. Addressing these persistent cancer health disparities poses a significant challenge for researchers and policymakers.

Access and utilization of health services ranging from screening to treatment are perhaps the most readily identifiable causes of disparities in cancer outcomes. In the U. S., access is greatly affected by insurance coverage, and while nationally 14% of the population is uninsured, 37% of Latinos lack insurance, and 20% of African Americans are uninsured (122, 123). Even when the lack of insurance does not create a barrier to care, the availability of local providers and healthcare facilities can create barriers. Furthermore, when care is available, social and cultural biases can often inhibit patients from accessing care (124), and when individuals seek care, the care they receive can often depend on their race (125). Lastly, most cancer therapies are derived from focused research that culminates in clinical trials that determine whether experimental therapies should be approved for general use, and while enrollment in cancer trials is low for all patient groups, racial and ethnic minorities, and the elderly are significantly under-represented in cancer clinical trials. This means that therapies often enter widespread use without thorough evaluation of their efficacy in all populations.

While access to healthcare can help explain differences in treatment outcomes between certain groups, many cancer disparities emanate from differences in cancer incidence. Groups vary in both genetic and behavioral risk profiles, and it can often be difficult to untangle the effects of the two since some racial and ethnic groups share not only similar inherited genes, but also similar cultural practices like diet. Increased access to genetic sequencing should make it easier for future researchers to tease apart the contributions of the two.

Mutations in the BRCA genes are but one example of a genetic risk factor that is more prevalent in a specific ethnic group than others, which creates cancer disparities. For example, approximately 2.0-2.5% of women with Ashkenazi Jewish ancestry have one of three specific mutations in the *BRCA1* and *BRCA2* genes, which is about five times the prevalence of this mutation in people of other ethnicities (126). As a result, 60% of this population will develop breast cancer in their lifetimes as compared to the 12% of women in the general population who will do the same (127, 128).

Continued research will undoubtedly reveal other similar genetic risk factors that disparately either drive cancer incidence or inhibit effective treatment. Where genes are not the cause of disparities, research will still be critical to identify causes and develop sound evidence-based interventions to address cancer health disparities.

Asian Americans are twice as likely to suffer from liver and stomach cancer than the general population.

People of Ashkenazi Jewish ancestry have an increased risk of several types of cancer, including breast, ovarian, pancreatic and colorectal cancers.

African American men and women have higher rates of colorectal cancer and are more likely to die from it than their white counterparts.

Lung cancer rates among Southeast Asians are 18% higher than among non-Hispanic white Americans.

Most cases of lung cancer among East Asian women occur among never smokers, suggesting that genetic and/or environmental risk factors are involved.

Triple negative breast cancer is significantly higher in African American women than all other ethnicities (138, 139).

Hispanic and African American women have a much higher incidence of cervical cancer than white women.

Women of Ashkenazi Jewish ancestry are also about five times more likely to have one of three specific mutations in the *BRCA1* and *BRCA2* genes than people of other ethnicities (126).

The incidence rate for leukemia is approximately 17% higher among Hispanic children than non-Hispanic white children.

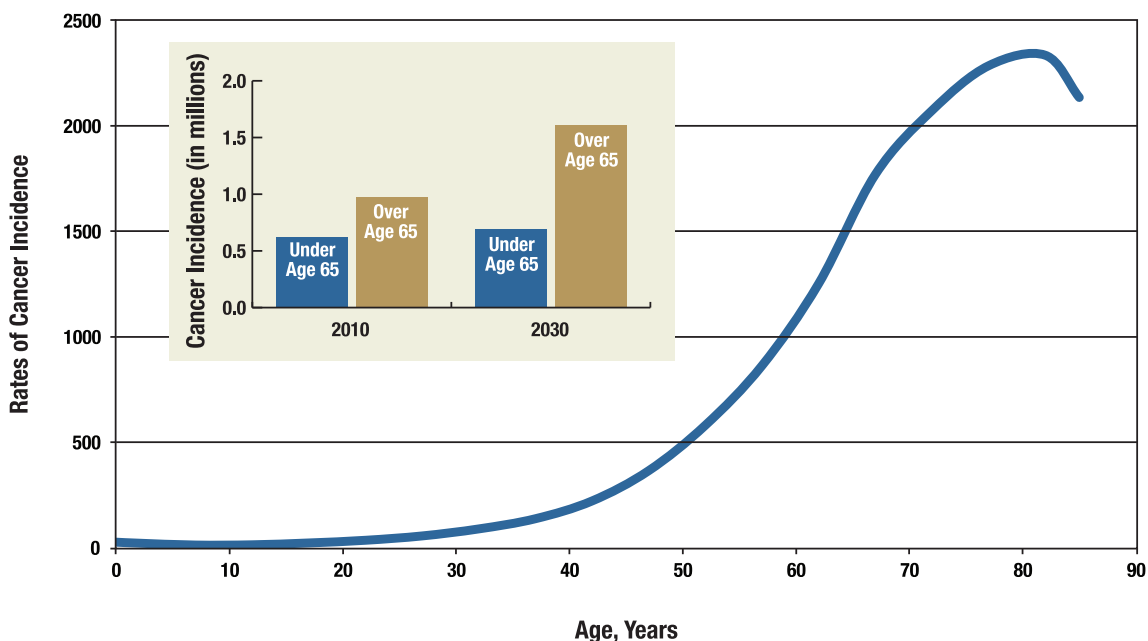
American Indians/Alaska Natives have higher rates of kidney and renal pelvis cancer than their white counterparts.

African American men have far higher death rates from prostate cancer than any other racial or ethnic group(3).

American Indian/Alaska Native men are 80% more likely to have liver and intrahepatic bile duct cancer than non-Hispanic white men.

American Indian/Alaska Native men are nearly twice as likely to have and die from stomach cancer as non-Hispanic white men.

## Differences in Cancer Incidence and Mortality



**Figure 1: Aging Baby Boomers Predicted to Drive up Incidence of Cancer.** The majority of all cancer diagnoses are made in those over the age of 65 (blue line)(4). In 2010, individuals in this age group made up 13% of the U.S. population (5). In 2030, when all of the baby boomers will be age 65 or older, this segment will be nearly 20% of the population (6). This change will be a big factor in pushing up the total numbers of cancers diagnosed each year, with a 67% increase in cancer incidence anticipated for those over the age of 65 (B)(7).

making cancer the most costly disease to the Nation. Unless more successful preventive interventions, early detection tools and treatments can be developed, this cost will rise dramatically during the next two decades.

Cancer prevention, in particular, is an area of great promise because research has shown that about two out of every three cancer deaths in the U.S. are due to preventable causes (3). Almost one third are caused by tobacco use; about one third are related to patients being overweight or obese, physically inactive and consuming a diet poor in nutritional value; some are caused by infectious agents for which we have vaccines; and many of the deaths from melanoma are a result of prior excessive sun exposure or use of indoor tanning facilities. Developing evidence-based approaches to cancer prevention, including research related to tobacco cessation, remains an area of active investigation.

The number of newly diagnosed cases of cancer is rising not just in the U.S., but throughout the world, with global numbers predicted to rise from 12.7 million new cases in 2008 to 22.2 million by 2030 (9). Without major new advances in cancer research to facilitate the successful development of effective preventive interventions and treatments, this will translate into more than 13 million lives claimed by cancer in 2030 (10). Moreover, of all causes of death worldwide, cancer has the greatest economic impact from premature death and disability. This global economic toll is 20%

higher than that from any other major disease, at \$895 billion in 2008 (11), not including the direct costs of treating cancer. Collaborations between U.S. cancer researchers and the international cancer research community are essential to sharing knowledge and leveraging resources to hasten the reduction in cancer burden and improvement of global health.

At this point in time, continued progress in life-saving cancer research is in jeopardy. NIH and NCI budgets have been declining since 2003, and many promising scientific projects are not being funded. This report captures many of the remarkable recent advances that are the direct result of the dedicated work of thousands of researchers who are now poised to exploit the current scientific momentum to save more lives from cancer. This will only be achieved if Congress provides the required support for cancer research.

**DEATH RATES FOR PANCREAS (1990-2008)**



EST. 2012 INCIDENCE = 43,920 • DEATHS = 37,390



# Why Cancer Research?

Research is our best defense against cancer. The Nation's investments in cancer research and biomedical science during the past four-plus decades have produced remarkable progress in our understanding of the events which initiate a number of cancers at the molecular, cellular and tissue levels. Advances in cancer research are now transforming patient care. We would not be on our current path to revolutionizing cancer care if not for the extraordinary endeavors of individuals working in numerous research disciplines and technologies.

Today, we know that because cancer is extremely heterogeneous, it is in fact not a single disease, but likely consists of over 200 diseases. Further, we are beginning to understand that due to this heterogeneity, nearly all cancers are comprised of a number of different cancer subtypes, meaning that every person's cancer is unique in its composition. Despite the apparent complexity that this diversity brings, decades of research have established that there are a number of basic biological principles that underpin cancer initiation, growth and spread to other sites in the body.

One of the most fundamental traits of cancer cells is their ability to multiply uncontrollably. Normal cells only proliferate when the balance of numerous factors instructs them to do so, by progressing through a process called the cell cycle (see **Fig. 2**, p. 20). Various inputs determine whether or not a cell will enter this cycle; these include the balance of growth-stimulating and growth-suppressing factors; the energy state of the cell, including nutrient and oxygen levels; and the status of the environment that surrounds the cell, called the microenvironment. This biological system is dysfunctional in cancer cells.

A second characteristic central to cancer cells is their ability to invade and destroy normal tissue surrounding them and to move to and grow in other areas of the body, called metastasis. Metastasis is the most lethal attribute of cancer cells. It is responsible for more than 90% of the morbidity and mortality associated with cancer (see **Sidebar on Metastasis**). Local invasion and metastasis are complex processes, fueled by changes in the cancer cells and in their interactions with their environments.

The development of cancer is largely due to the accumulation of genetic changes that lead to malfunctions in the molecular

## Metastasis

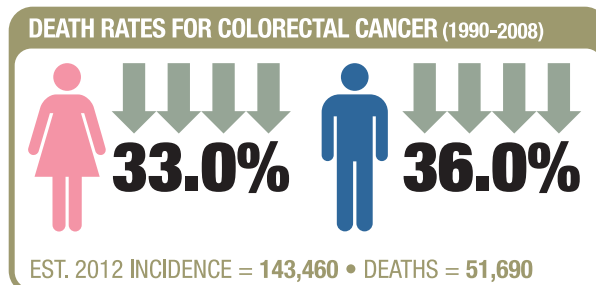
Metastasis is the spread of cancer cells from a primary tumor to other areas of the body where they establish new tumors. It is responsible for more than 90% of the morbidity and mortality associated with cancer. Studying the fundamental properties of metastasis is essential to conquering cancer, because it is only through research that we will be able to identify important targets for the development of new therapies to prevent or treat metastasis, and learn how to predict who will develop metastatic cancer and require these therapies.

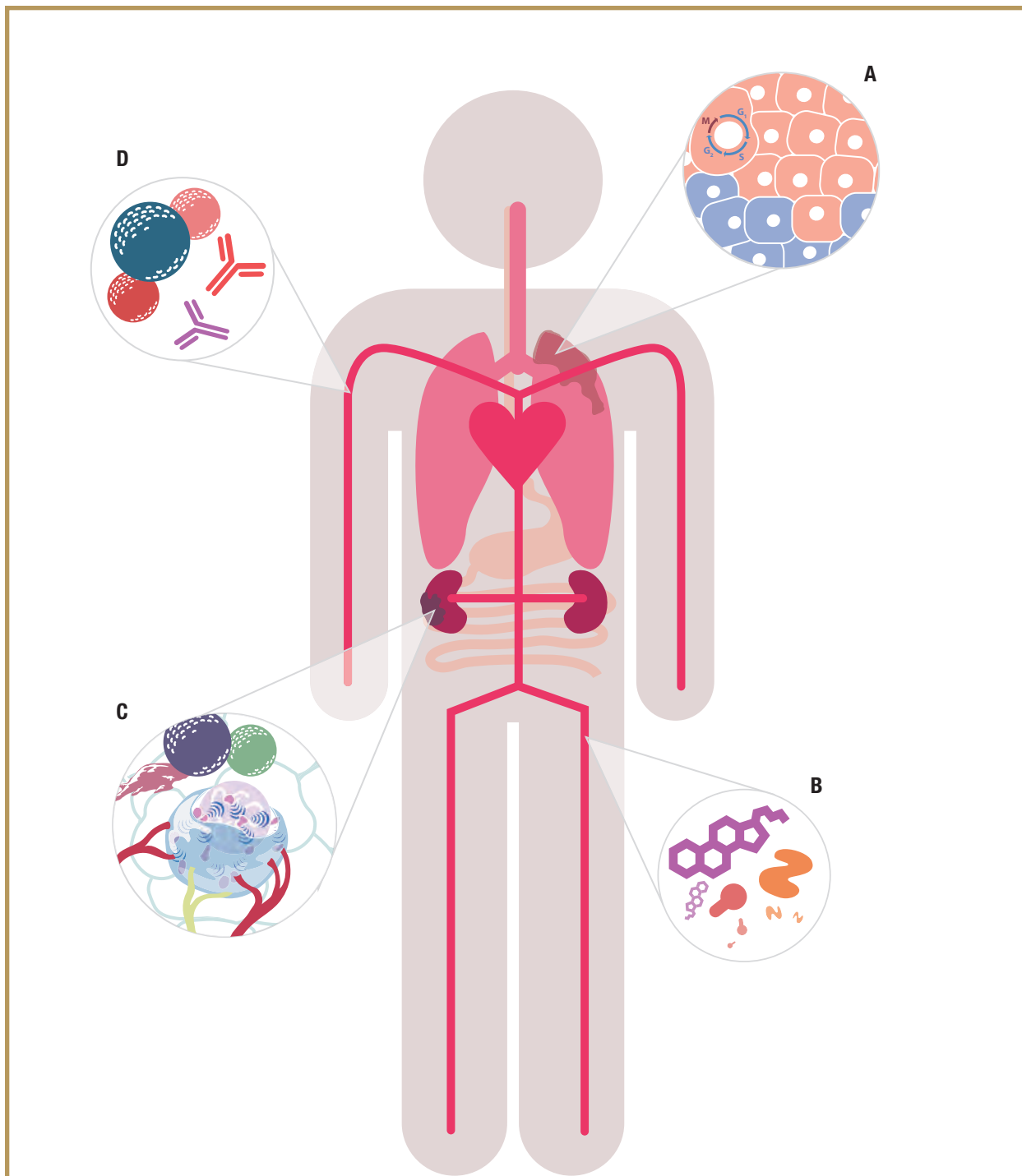
Already we have learned a great deal about this deadly process, some of which explains why metastatic disease is so difficult to treat. For example, virtually every step of the metastatic process can be achieved through multiple different means, giving the cancer cells many opportunities to metastasize. This also means that blocking only one pathway therapeutically will not be sufficient. In addition, we know that cancer cells can travel to other parts of the body and then lie dormant in this new location for years, becoming active again later in life. A greater understanding of the factors that contribute to tumor cell dormancy could lead to the development of new therapies that have the potential to prevent these dormant cells from reawakening.

Metastatic disease is a dire situation that requires an immediate and complete therapeutic response in order to prevent almost certain death. While recent research has revealed that there is a genetic basis for susceptibility or resistance to metastasis, creating new avenues for the development of effective therapies, much more work is needed if we are to develop a comprehensive understanding of this complex process and make significant progress against cancer and toward saving lives.



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.





**Figure 2: 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 (A and C)(see **Sidebar on The Genetic Basis of Cancer**). Uncontrolled proliferation occurs when normal control of a tightly regulated cellular process called the cell cycle is lost (A). Interactions between cancer cells and their environment also 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 to bring nutrients as well as escape to distant sites (metastasize) (C) and its capacity to manipulate the immune system (D).

machinery of cells, permitting them to survive when normal cells would die and to multiply uncontrollably and metastasize. In addition, interactions between cancer cells and their microenvironment profoundly affect these same processes. Cancer-influencing factors that comprise the tumor microenvironment include the matrix of proteins outside the cancer cell that support the structure and function of the tissue in which the cancer is growing; the creation of new blood and lymphatic vessels; hormones; nutrients; and the immune system (see **Fig. 2**, p. 20).

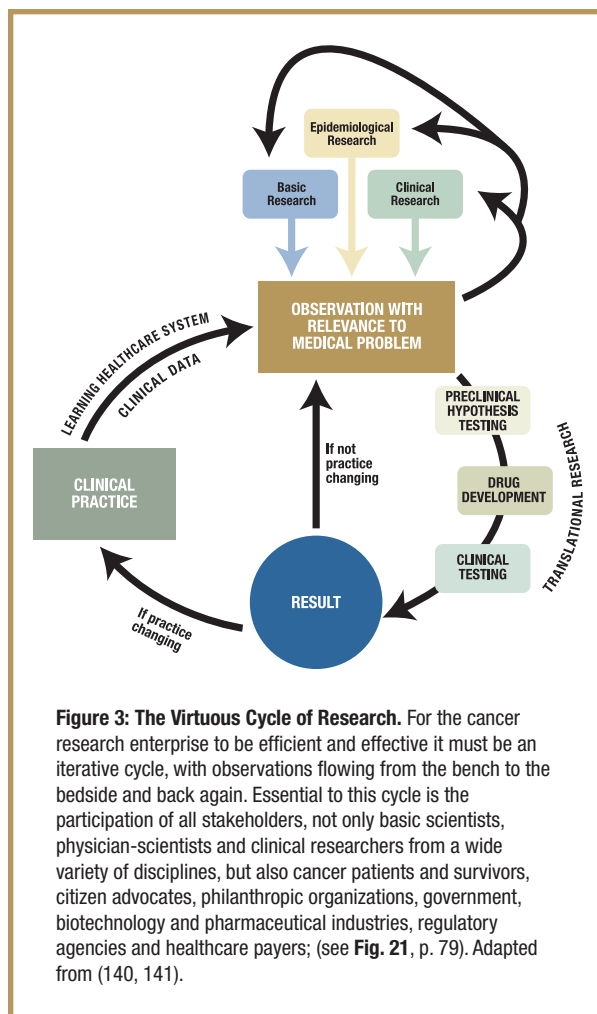
Insight into the importance of inflammation, established by certain cells of the immune system, in promoting cancer progression has increased dramatically in the past few years. Persistent inflammation—for example, that driven by infection with hepatitis B virus (HBV) or hepatitis C virus (HCV), or by continual exposure to toxins like alcohol or asbestos—has been known for some time to create an environment that fosters cancer cell survival, proliferation, local invasion and metastasis. More recently, it has become apparent that chronic inflammation in an organ or a region of the body enables cells in that area to acquire the characteristics needed for cancer formation.

In addition to better understanding the concept of tumor-promoting inflammation, the last several decades of research have also established the importance of the components of the immune system that participate in antitumor defense. That knowledge has stimulated developments of drugs designed to boost patients' antitumor immunity.

Although we have learned a great deal about the unifying principles that underpin cancer, translating this knowledge into cures remains challenging because of the diversity of cancer types. Currently, many areas of research are rapidly evolving, in part as a result of technological advancements that are increasing our ability to probe the genetic and molecular defects that drive cancer. With continued federal investments, these endeavors will yield new discoveries that improve the ways we prevent, detect, diagnose and treat cancer.

## Cancer Research: From Concept to Patient and Back Again

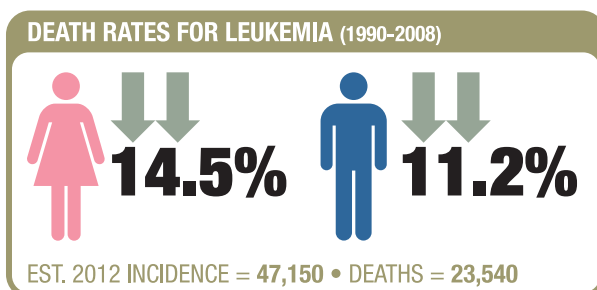
If cancer research is to be truly successful, it must be an iterative cycle, with observations flowing from the bench to the bedside and back again (see **Fig. 3**). The participation of patients and their health care providers is essential to this cycle because observations made in clinical trials also help define areas for future study, including the identification of new drug targets and the refinement of treatment. Finally, cancer research does not operate in isolation from other fields of research. Insights into the biology of cancer and the identification of ways to prevent, detect, diagnose and treat its many forms offer new ideas for the conquest of other diseases.

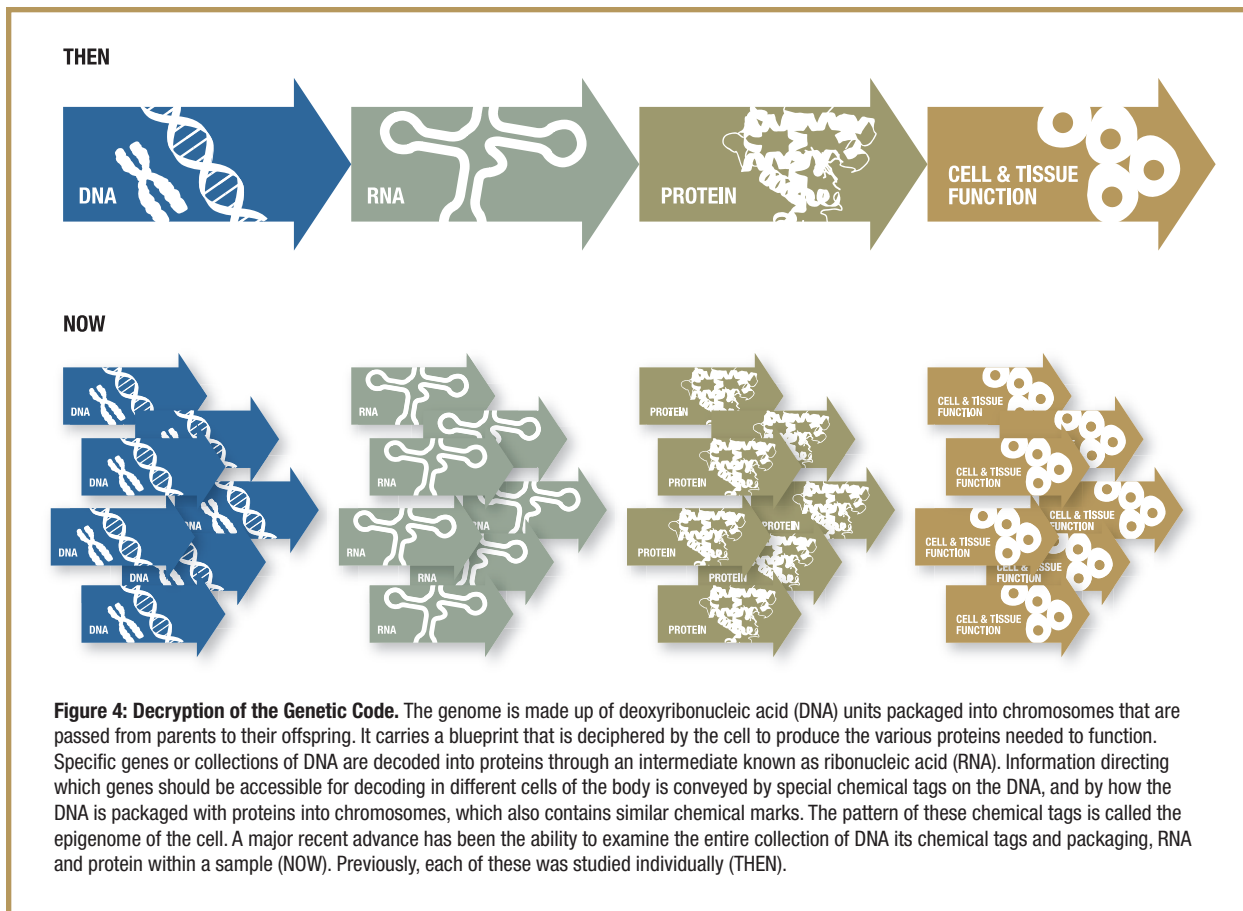


**Figure 3: The Virtuous Cycle of Research.** For the cancer research enterprise to be efficient and effective it must be an iterative cycle, with observations flowing from the bench to the bedside and back again. Essential to this cycle is the participation of all stakeholders, not only basic scientists, physician-scientists and clinical researchers from a wide variety of disciplines, but also cancer patients and survivors, citizen advocates, philanthropic organizations, government, biotechnology and pharmaceutical industries, regulatory agencies and healthcare payers; (see **Fig. 21**, p. 79). Adapted from (140, 141).



**1 out of 2 men** and  
**1 out of 3 women**  
will be diagnosed with cancer  
in their lifetimes.





The concept of taking an observation, making a discovery, turning it into a tangible tool, drug or agent to be studied in the clinic, testing the discovery in the clinic and ending up with a viable approach for cancer prevention, detection, diagnosis or treatment is sometimes called target-based discovery. It is not the only strategy for developing new ways to reduce the tremendous burden of cancer, but increasingly the advances reaching the clinic are the result of target-based discovery programs (see **Making Research Count for Patients**, p. 46). The following focuses on some of the more frequently used ways in which those involved in basic and clinical cancer research take an idea all the way to the patient.



**Epidemiologists** study the frequency, distribution and patterns of risk factors, diseases and health outcomes in populations to better understand the associations, interactions and causal relationships between them. Epidemiologists can be subdivided based on the information that they gather from the group(s) being studied; for example, molecular epidemiologists collect and analyze genetic and molecular information.

### Experimental Models of Cancer

In the laboratory, researchers study patient samples as well as cells and animals that mimic what happens in healthy and cancerous conditions.

A wide variety of cell types are used in cancer research. Some cells can be grown continuously in the lab in such a way that each is genetically identical, and these are called cell lines. Others are primary cells, which are genetically diverse because they are obtained directly from tissues. The tissues can be healthy or cancerous and isolated from a human or animal. Cells can be studied in dishes in the laboratory or after having been transferred into animals.

Mice constitute the most commonly utilized animal models in all areas of cancer research. Zebrafish have recently emerged as a useful model for melanoma, the most deadly form of skin cancer, and for leukemias. Other animals are also used, but largely for specific cancer types. For example, because some dog breeds naturally develop certain cancers, they are good models for studying the equivalent human diseases.

## Probing Cancer Models: Generating and Testing Ideas

The study and manipulation of these models—for example, exposing them to a potential new drug—can help identify useful approaches for cancer 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.

The genetic code carries a blueprint that is deciphered by the cell to produce the various proteins that it uses to function (see **Fig. 4**, p. 22). Some genetic alterations result in the generation of abnormal proteins that can fuel the development of cancer. Alternatively, they may lead to the loss of other critical proteins that usually maintain normal cellular functions (see **Sidebar on the Genetic Basis of Cancer**). Tremendous technological advances in recent years have made it possible to rapidly sequence the entire genome of a cancer to reveal which genetic alterations are present. Furthermore, these technologies can also detect changes in the cancer's epigenome, which is how the DNA is modified and packaged into chromosomes.

Whether or not the observed genetic and epigenetic changes contribute to cancer can be examined further by engineering cells or animals to express the modification and by observing the resultant changes in cell or animal behaviors. Previously, researchers studied individual pieces of DNA, proteins and cell metabolites as they pertain to cell function. Now, as a result of innovative large-scale approaches, researchers can study the entire set of DNA, proteins and metabolites in a sample. These new approaches complement more traditional biochemical methods to rapidly enhance our understanding of the structure and function of cancer-associated proteins and their effects on cell behavior.

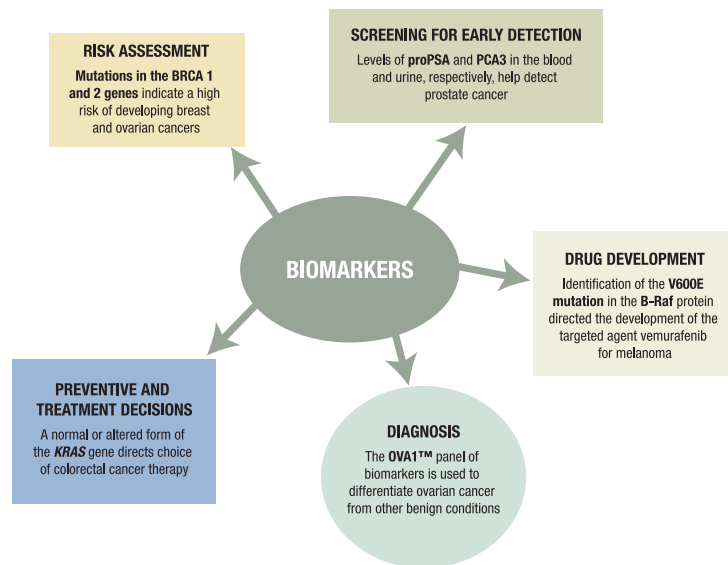
## The Genetic Basis of Cancer

One of the greatest advances in cancer research was the discovery that changes, or mutations, in genes can cause cancer. The “genetic code”, carried in deoxyribonucleic acid (DNA) units called bases is packaged into chromosomes that are passed from parents to offspring. The entirety of a person's DNA is called a genome. The genetic code within our genome is decoded to produce the various proteins that our cells use to function; (see **Fig. 4**, p. 22).

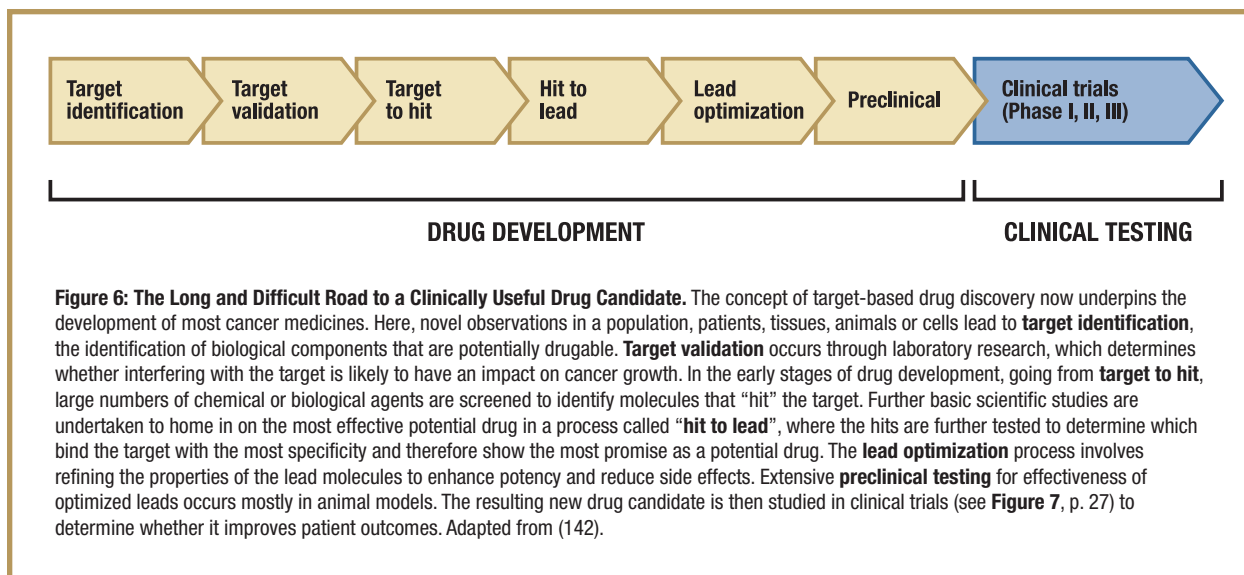
In cancer, chromosomes sometimes break and recombine causing large-scale changes within the genome. Genes can also be altered by single mutations in DNA units. Over the years, researchers have determined that cancer-associated genetic mutations are often found in one of two classes of genes: oncogenes and tumor suppressor genes. Oncogenes can drive the initiation and progression of cancer by producing abnormal proteins that permit cancer cells to ignore normal proliferative regulatory signals. Tumor suppressor genes encode proteins that normally stop the emergence of cancer. Mutations in these genes result in proteins that fail to function properly, enabling cancer cells to proliferate unchecked.

The correlation of genetic mutations with specific malfunctions of cellular molecular machinery that result in cancerous cell behaviors has provided the impetus for the development of many molecularly targeted cancer drugs, bringing the prospects of a new day for cancer prevention, detection, diagnosis and treatment closer to reality.

**Figure 5: Follow the Signs to Cancer Prevention, Detection, Diagnosis and Treatment.** Biomarkers are defined as cellular, biochemical and molecular (including genetic and epigenetic) characteristics by which normal and/or abnormal processes can be recognized and/or monitored. Biomarkers are measurable in biological materials, such as in tissues, cells, and/or bodily fluids. Depicted are examples of biomarkers in clinical use to help assess a person's cancer risk, detect a growing cancer, make a cancer diagnosis, identify those patients most likely to benefit from a specific molecularly targeted therapy and modify treatment decisions. In some cases, the biomarker used to identify those patients most likely to benefit from a specific molecularly targeted therapy is the same biomarker used in the process of developing the drug. The identification of additional biomarkers to further improve cancer prevention, detection, diagnosis and treatment is an area of intense investigation.







Laboratory studies enable researchers to identify changes in genes and proteins linked to cancer. Converting these discoveries into a tool, drug or agent to be tested in the clinic can take many different forms. Some of these validated discoveries identify biological indicators, or biomarkers, which may be clinically useful (see **Fig. 5**, p. 25), while others can be developed into a potential drug (see **Fig. 6**).



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

### Moving Cancer Research into the Clinic

Before a tool, drug or agent developed through many years of work in the laboratory can be used routinely in patient care, it must be rigorously tested in clinical trials, which provide each patient with the best care available. This step from the bench to the bedside involves a vast array of approaches. The discussion here only highlights some examples of how this step toward reducing the burden of cancer is implemented.



**Clinical researchers** study a particular person or group of people or use materials from humans, such as their behavior or samples of their tissue, to learn about disease and the way the healthy body works.

In the case of a potential therapeutic for cancer treatment, clinical trials with increasing numbers of patients are undertaken to determine the safety and effectiveness of the potential therapy (see **Fig. 7**, p. 25). Individuals participating in clinical trials are monitored extremely closely. For example, levels of known cancer markers in the urine or blood can be regularly checked to provide information as to whether or not the drug is effective. Currently, however, the predominant criteria used to determine whether a new drug for cancer treatment benefits patients are: Does it stop tumor growth or reduce its size? Does it increase the length of time to renewed growth or spread, as assessed by tumor imaging? And does it increase patient survival time?

In many clinical trials, tumor imaging is done using computed tomography (CT) scanning, but other technologies can be used, such as magnetic resonance imaging (MRI) and positron emission tomography (PET) using a radiolabeled tracer called

“In this time of severe budget constraints, Americans need to know that today’s basic research is the engine that powers tomorrow’s therapeutic discoveries. They need to know that basic research is the type of science that the private sector, which requires rapid returns on investment, cannot afford to fund. They need to know that, because it is impossible to predict whence the next treatment may emerge, the nation must support a broad portfolio of basic research.”

**Francis Collins, M.D., Ph.D.,**  
Director, National Institutes of Health



<sup>18</sup>fluorodeoxyglucose (FDG; see Fig. 8, p. 26). As progress is made in enhancing imaging capabilities, these scans can be incorporated into clinical trials. It is hoped that as advances are made, they can be used to shorten the process of drug development, with significant reductions in tumor burden visible by imaging techniques being used as a measure of drug effectiveness. This is a very active area of cancer research, with multiple other approaches being actively assessed for their utility in the same context.

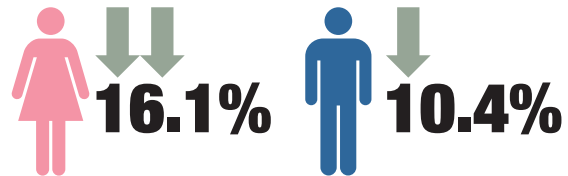
### Clinical Outcomes Go Back to the Laboratory

It is vital that what happens at the bedside is not the end of the cancer research trail. Even if clinical studies indicate that the 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 (see Fig. 3, p. 21 and **Sidebar on Learning Healthcare Systems**, p. 27). For example, some tumors learn to bypass initially efficacious treatments, and how that happens needs to be determined in order to develop new and improved therapies. In cases where there is no immediate gain observed in the clinic, the knowledge amassed during the trial can be probed for insights into why and how the treatment failed to have the expected effects and how to improve upon it.



**Physician-scientists** care for patients and also work in a laboratory. In the laboratory, physician-scientists may perform clinical research or basic research.

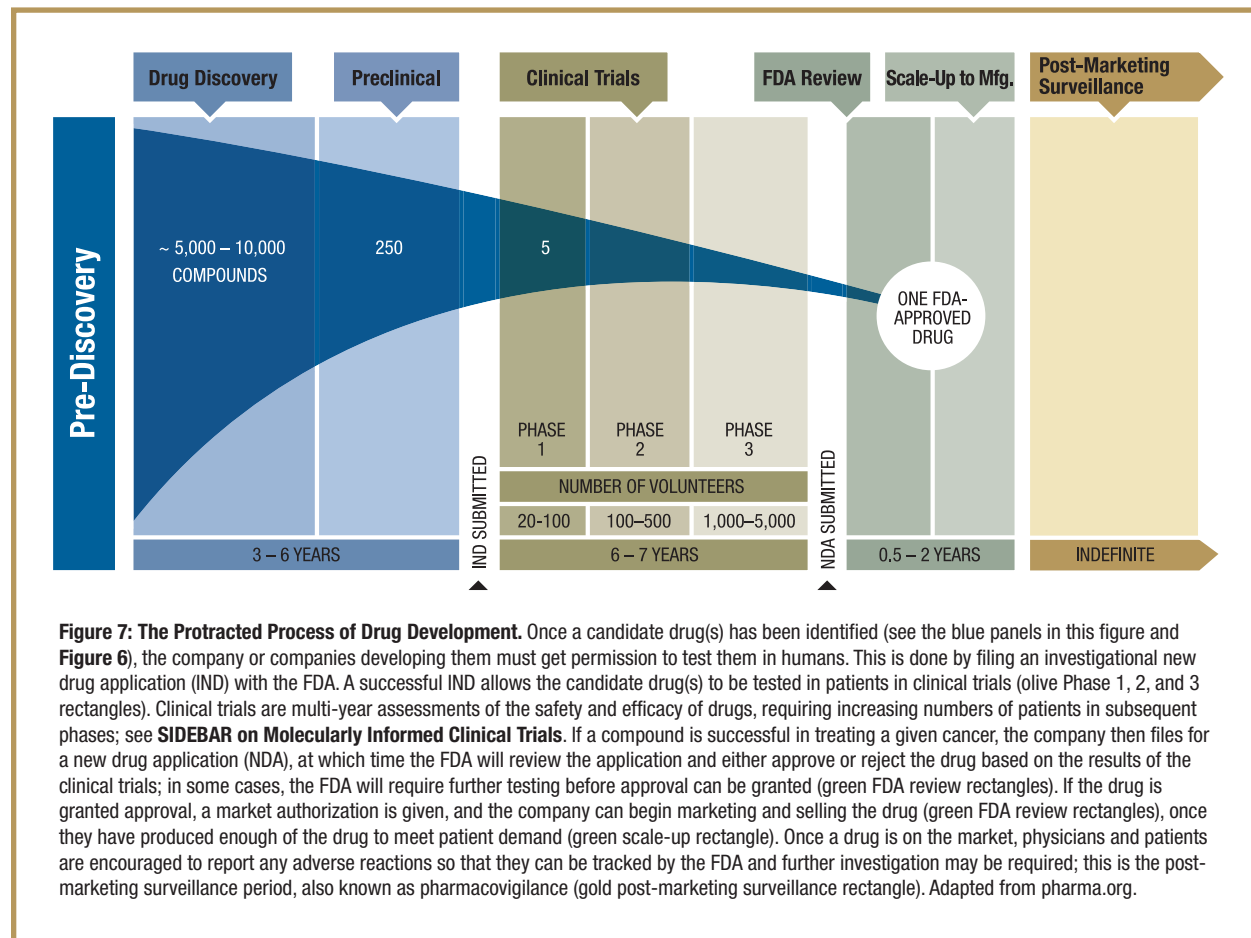
### DEATH RATES FOR MYELOMA (1990-2008)



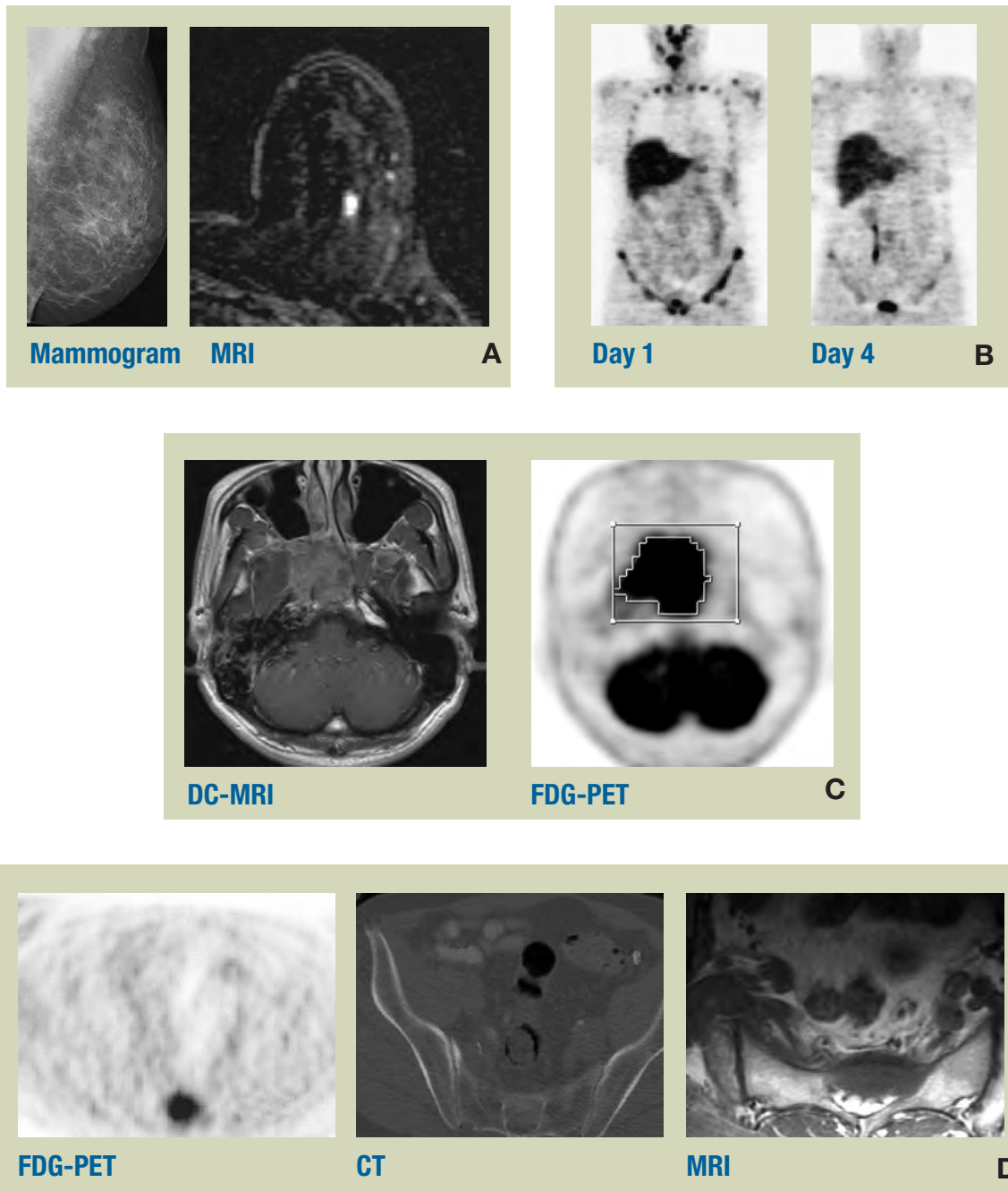
EST. 2012 INCIDENCE = 21,700 • DEATHS = 10,710



that clinical trials are an essential part of drug development? They represent the best care a patient can receive, but fewer than **5%** of adults diagnosed with cancer participate in a clinical trial.

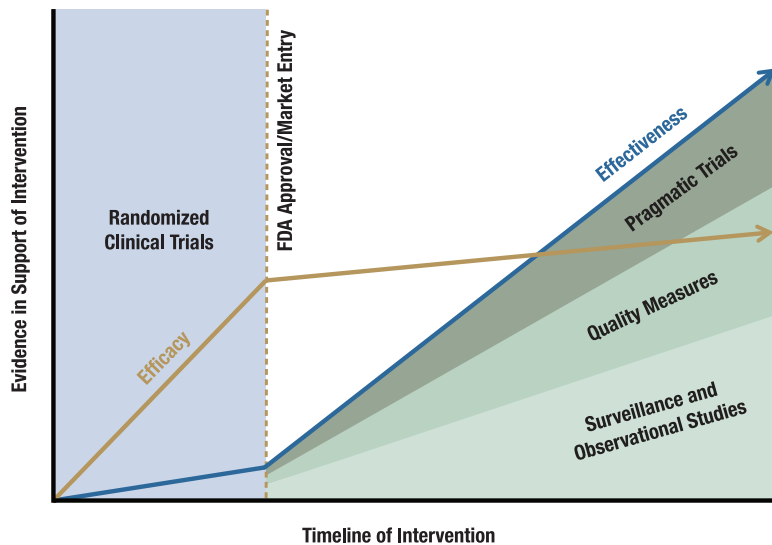


**Figure 7: The Protracted Process of Drug Development.** Once a candidate drug(s) has been identified (see the blue panels in this figure and Figure 6), the company or companies developing them must get permission to test them in humans. This is done by filing an investigational new drug application (IND) with the FDA. A successful IND allows the candidate drug(s) to be tested in patients in clinical trials (olive Phase 1, 2, and 3 rectangles). Clinical trials are multi-year assessments of the safety and efficacy of drugs, requiring increasing numbers of patients in subsequent phases; see **SIDEBAR on Molecularly Informed Clinical Trials**. If a compound is successful in treating a given cancer, the company then files for a new drug application (NDA), at which time the FDA will review the application and either approve or reject the drug based on the results of the clinical trials; in some cases, the FDA will require further testing before approval can be granted (green FDA review rectangles). If the drug is granted approval, a market authorization is given, and the company can begin marketing and selling the drug (green FDA review rectangles), once they have produced enough of the drug to meet patient demand (green scale-up rectangle). Once a drug is on the market, physicians and patients are encouraged to report any adverse reactions so that they can be tracked by the FDA and further investigation may be required; this is the post-marketing surveillance period, also known as pharmacovigilance (gold post-marketing surveillance rectangle). Adapted from pharma.org.



**Figure 8: Visualizing Cancer.** Imaging is an increasingly essential part of modern cancer care, from routine screening and prevention to informing diagnoses. More recently, imaging is being used to monitor response to therapy both in the clinic and during drug discovery. Not all imaging, however, provides the same quantity or type of information. In the example shown, a routine mammography (A, mammogram) detected no cancer, while MRI detected a tumor in the same breast (A, MRI) (143). Likewise, in this example FDG-PET revealed a bone metastasis (D, FDG-PET), whereas the CT scan did not (D, CT) and the MRI analysis was unclear (D, MRI) (144). New types of imaging like FDG-PET are better able to detect metastases (B, day 1) and show the patient's tumor's rapid response to therapy (B, day 4) (145). Increasingly, different types of imaging are being combined to provide the most complete information possible. For example, the use of double contrast-MRI together with FDG-PET (C) reveals the precise location and size of the tumor (146).

## Learning Healthcare Systems



### Accumulation of evidence in a learning healthcare system.

Evidence for efficacy is primarily generated in a pre-market setting, typically based on randomized clinical trials. Evidence for effectiveness accumulates over a longer period of time, after market entry using a variety of study methodologies. The learning healthcare system, enhanced by electronic medical records and HIT, will dramatically facilitate the generation of evidence of effectiveness. *Adapted from IOM Roundtable On Value & Science-Based Health Care, "The Learning Health Care System and its Innovation Collaboratives: Update Report 2011"*

Learning healthcare systems generate and collect evidence from the delivery of health care in everyday clinical settings. This evidence is used to determine which interventions work best and for whom when placed into broad clinical practice, with the results feeding back into the data system to continually and iteratively improve clinical care delivery. Thus, learning healthcare systems complement the clinical trials process and its goals by examining the effectiveness of interventions or their utility in a real-world setting, rather than their efficacy or use in the restricted populations and idealized settings involved in clinical trials. In addition, although regulatory agencies like the FDA require proof of efficacy for drugs and biologics before they can be used clinically, other interventions such as imaging, surgery or off-label drug use do not require the same scientific scrutiny for efficacy, let alone demonstrations of effectiveness, before entering widespread use. Learning from everyday healthcare delivery is becoming a reality because of the contributions of contemporary health information technology, informatics, and the availability of real-time data and analytics. The continual evaluation and modification of healthcare interventions enabled by a learning healthcare system ensure that the care delivered to patients is effective and efficient, saving patients unnecessary treatment, wasted time and added costs.

### Tools Used in a Learning Healthcare System:

- **Health Information Technology (HIT):** Data collection and analysis infrastructure that enables digital recording of patient information, diagnosis and treatment history along with outcomes. These systems allow easier and more widespread data access, opening up the possibility of secondary data use for research purposes.
- **Observational studies:** Research that infers links between treatments and outcomes based on natural—as opposed to experimental—variations in treatment delivery. These analyses are often applied in retrospect in a learning healthcare system
- **Pragmatic clinical trials:** Randomized experiments designed to test effectiveness of an intervention in normal clinical settings with attendant natural confounding factors.
- **Registries:** Databases organized around specific diseases or interventions (e.g., cancer or implanted defibrillator) that record patient and outcome information.
- **Patient-reported outcomes:** Effects of treatment as reported directly by a patient (e.g., pain, fatigue, mood, mobility, quality of life, etc.)
- **Quality measures:** Standardized metrics that indicate the degree of attainment of idealized treatment or outcomes goals.

# Prevention and Early Detection

Advances in cancer prevention and early detection have resulted in some of the greatest reductions in cancer mortality, and these have been achieved with remarkable impact by translating scientific discoveries into actions by two complementary strategies: public health initiatives involving education and policy, and personalized initiatives applied in the clinic. Public health measures have included public education regarding common cancer risks (such as physical inactivity and unhealthy diets) and policy development to minimize harmful exposures (such as smoke-free workplaces or asbestos remediation laws). Clinical preventive advances include improved screening practices (e.g., colonoscopy to detect and remove precancerous colorectal polyps) and targeted interventions (e.g., administering vaccines for infectious diseases associated with cancer risk).

This progress has come from decades of research that have led us to our current understanding of how cancers develop. We know that cancer is a complex process that takes place over a period of time, sometimes several decades. Most, if not all, tumors arise as a result of a series of changes in our genes or in the molecules that control how and when our genes are expressed. Our knowledge of the timing, sequence and frequency of the pivotal changes underlying tumor development is increasing, as is our insight into the specific implications of these changes. This provides us with unique opportunities for earlier identification of aberrations and therefore new prospects for developing the means to prevent cancer onset or to detect it and intervene earlier in its progression. We have also learned that cancer risk factors are varied, complex and interrelated, making it challenging, but not insurmountable, to deliver on the promise of cancer prevention. The identification of research priorities along with the necessary funding will help to accelerate progress in this important area.



**25%** of all deaths in the U.S. are caused by cancer.



**2/3** of cancer deaths are a result of preventable causes.

## To Know Your Risk, Know the Causes of Cancer

### Causes of Cancer You Can Avoid

Through the identification of numerous factors germane to cancer, scientists have come to the conclusion that almost two thirds of the more than 577,000 cancer deaths expected to occur in the U.S. in 2012 will be related to preventable causes [(3); see **Fig. 9**, pg. 29].

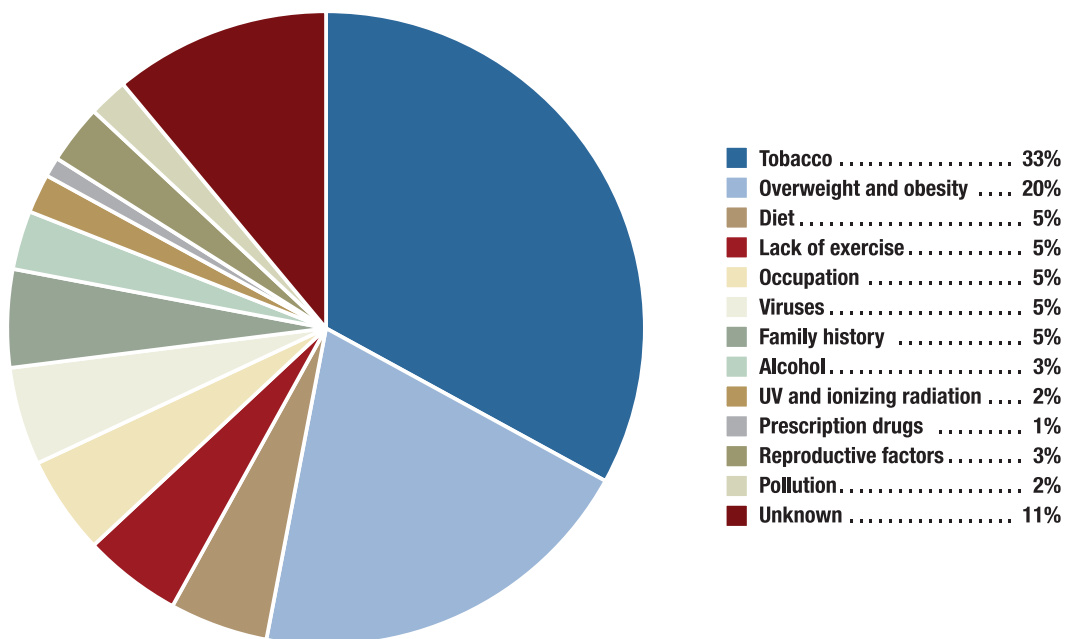
### *Tobacco Use and Cancer: Smoking-Gun Evidence*

One of the most successful examples of how scientific progress can inform public policy and educational efforts to measurably reduce cancer incidence and death rates is the 29% decline in lung cancer death rates among men that occurred between 1990 and 2008, which is directly attributable to the decrease in smoking prevalence (4). The scientifically established causal relationship between smoking and cancer, which began with epidemiological observations, gained prominence in the public arena in 1964 when the U.S. Surgeon General's Report on Smoking and Health was published (12). This report set in motion major U.S. policy changes, media campaigns and other measures to combat cigarette smoking (see **Fig. 10**, pg. 30). As a result of these efforts, the prevalence of smoking in the U.S. decreased from 42% of the population in 1965 to 19% in 2010 (13). 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, including head and neck, stomach, pancreas, cervical and other cancers (13), as well as to many other often fatal diseases.

Despite this progress, tobacco use will still be responsible for an estimated 30% of all cancer deaths that occur in the U.S. in 2012 (3). The Surgeon General's 31st report on tobacco (14), released in



### Estimated Percentage of Cancer Cases Caused by Identifiable and/or Potentially Preventable Factors



**Figure 9: An Ounce of Prevention is Worth a Pound of Cure.** The majority of cancers diagnosed today are a result of preventable causes, including smoking, obesity, poor dietary habits and physical inactivity. Many of these cancers could be prevented by modifying personal behaviors, although continued research is necessary to identify better ways to help address these behaviors. Data obtained from (147).

**DID YOU KNOW?**

that **17** cancers in addition to lung cancer are caused by smoking?

2010, concludes that there is no safe level of exposure to tobacco smoke. Yet, 70 million Americans regularly use tobacco products, and every day in 2010, 6,500 Americans aged 12 years and older smoked their first cigarette (15). 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. Although this has led to some important public health policies restricting smoking in public places, countless lives could be saved in the future through continued research to develop and implement effective tobacco prevention, cessation and control strategies such as those described in “Tobacco and Cancer: An AACR Policy Statement” [(16); see Fig. 11, pg. 30 and **Sidebar on Tobacco Tax**, pg. 31].

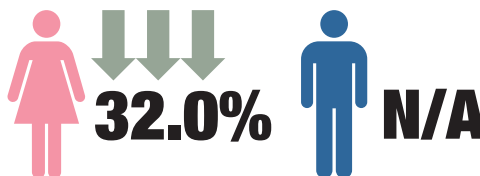
#### **Obesity and Physical Inactivity Weigh in on Cancer**

Data from numerous epidemiological studies have revealed that obesity is clearly linked to an increased risk for the

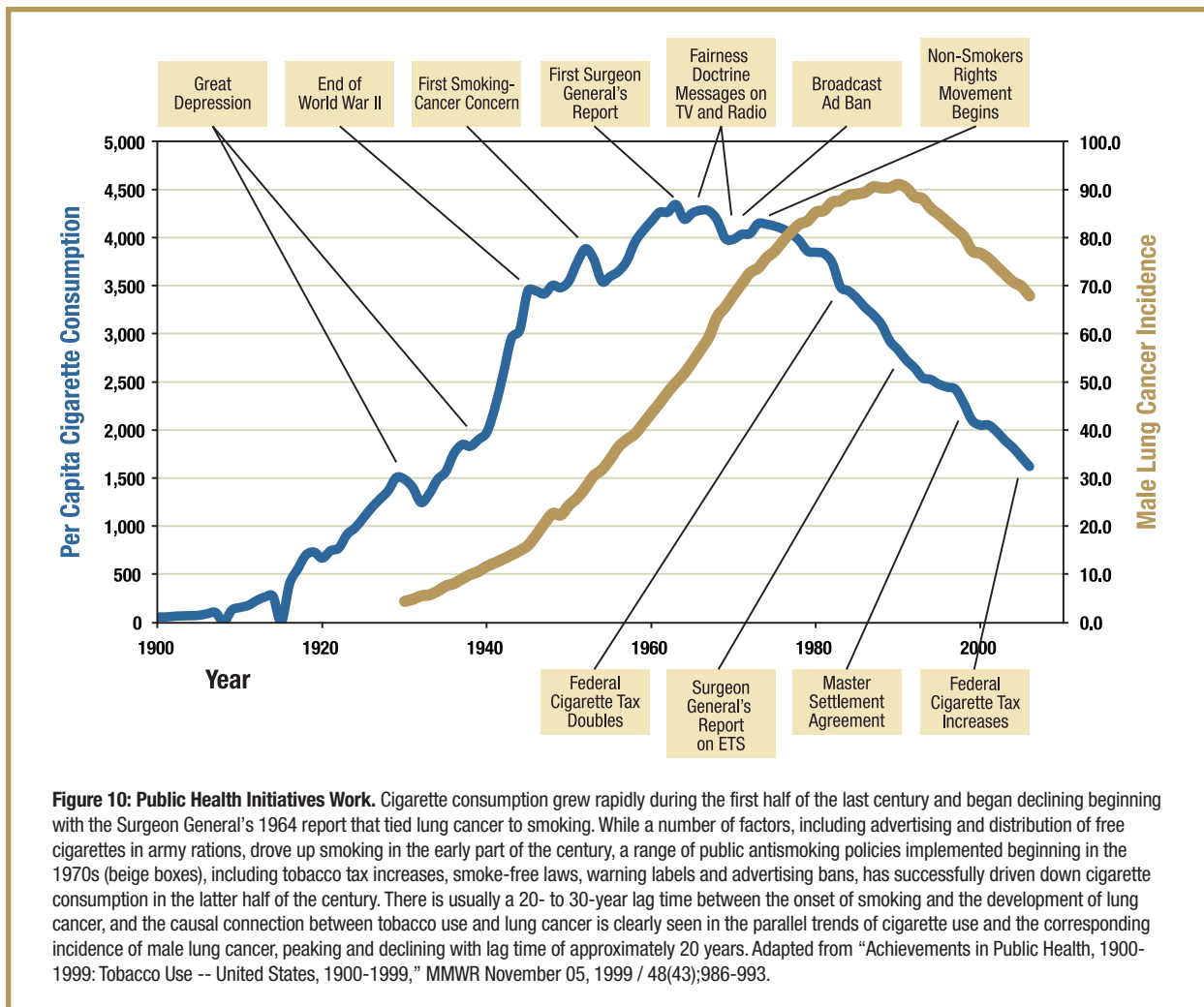
adenocarcinoma subtype of esophageal cancer and to pancreatic, colorectal, kidney, endometrial and postmenopausal breast cancers (8). Mounting evidence indicates that obesity is also associated with an increased risk for other cancers, including gallbladder and liver cancers (8). In line with the dramatic increase in incidence of obesity, incidence of several of these cancers, including pancreatic, kidney and liver cancers, have increased during the past 10 years (17). Independent of weight, a lack of regular physical activity is associated with an increased risk for colon, endometrial and postmenopausal breast cancers and also may be associated with lung, pancreatic and premenopausal breast cancers (8).

Obesity and physical inactivity are not just associated with increased cancer risk. They also negatively impact tumor recurrence, metastasis and patient survival for several types of cancers (17). Among patients with breast cancer (18), colorectal

#### DEATH RATES FOR BREAST CANCER (1990-2008)

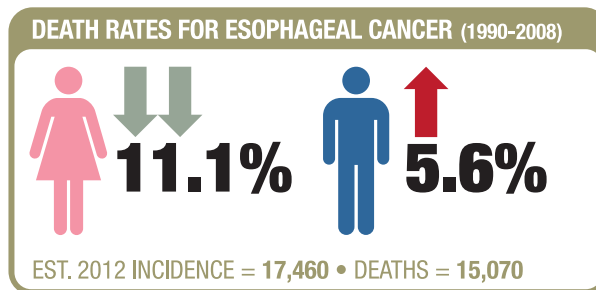


EST. 2012 INCIDENCE = 229,060 • DEATHS = 39,920



cancer (19) or prostate cancer (20), excess weight is associated with poorer outcomes; conversely, physical activity in patients with these diseases has been shown to improve outcomes (21, 22).

Although trends in the prevalence of obesity in the U.S. finally seem to be stabilizing, the number of individuals classified as obese is still at an all-time high. The latest figures indicate that more than 35% of adults and almost 17% of children and adolescents are obese (23). Similar proportions of individuals are considered physically inactive (17). These unparalleled levels of obesity and physical inactivity are important, avoidable causes of approximately one third of cancer deaths (3).



Research on a number of fronts indicates that if Americans were to modify their lifestyle to include regular physical activity, a balanced diet and a healthy weight, millions of people could reduce their risk of a cancer diagnosis. In recent years, several cities and states have adopted public policies to enable people to make healthier choices. However, additional research is required to develop and implement effective policy changes and media campaigns. In addition, continued fundamental research efforts are needed to better understand the biological mechanisms that link obesity and insufficient physical activity with cancer. Armed with this

\$

The estimated direct medical costs associated with treating cancer in 2007 were **\$103.8 billion** dollars and **\$123.0 billion** for costs associated with loss of productivity due to premature death.

## DID YOU KNOW ?

that increased risk for at least **8** cancers are linked to obesity and inactivity?

information, we may be able to develop clinical and pharmacological interventions to reduce the cancer burden resulting from obesity. Population and clinical studies that complement basic science endeavors will be necessary to determine the optimum body type, body composition and exercise program to reduce cancer risk and recurrence.

### ***Ultraviolet Light: Reflecting on a Cause of Cancer***

Researchers have clearly established a causal relationship between excessive exposure to ultraviolet (UV) light, which is a form of radiation emitted by the sun, sunlamps and tanning beds, and all three of the main types of skin cancer—basal cell carcinoma, squamous cell carcinoma and melanoma. Skin cancer is the most prevalent of all cancers in the U.S. Researchers have estimated that in 2012, there will be more than 2 million new cases of basal cell and squamous cell carcinoma (24) and 76,250 new cases of melanoma (3). The majority of non-melanoma skin cancers are highly curable when treated early, although a small fraction will progress to life-threatening metastatic tumors [see **Donna Johnson's Story**, p59; (25)]. Melanoma, although accounting for less than 5% of skin cancer cases, is the predominant cause of skin cancer death (3).

The overwhelming majority of skin cancers could be prevented if everyone avoided intense sun exposure. Thus, experts have recommended that people seek shade and limit time in the sun,

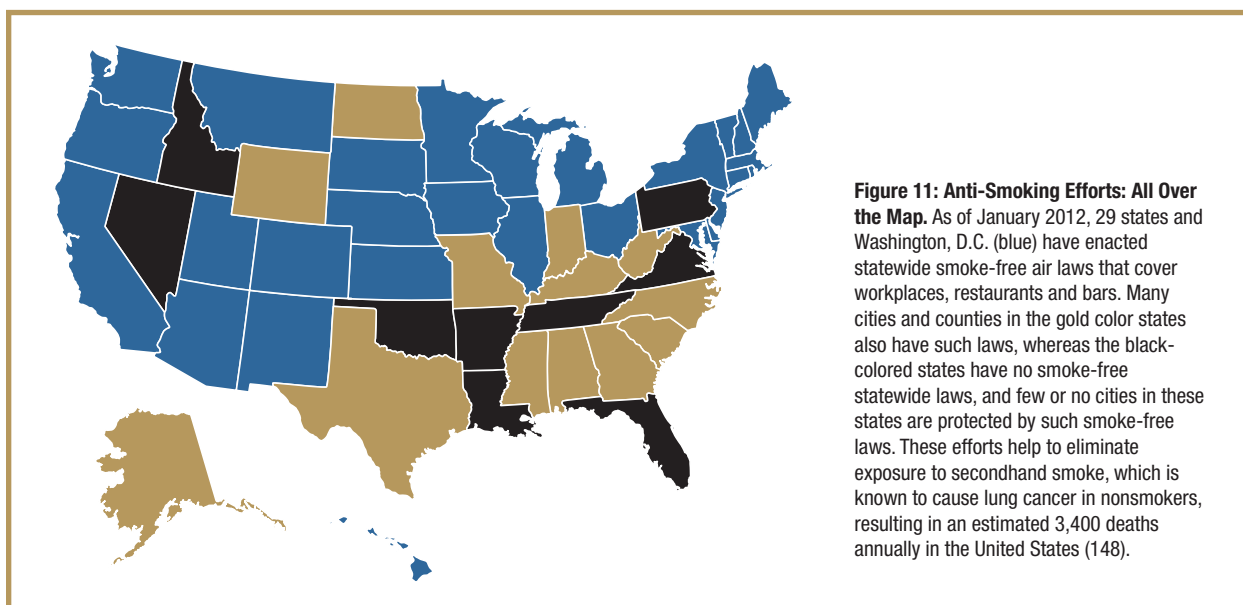
## Tobacco Tax

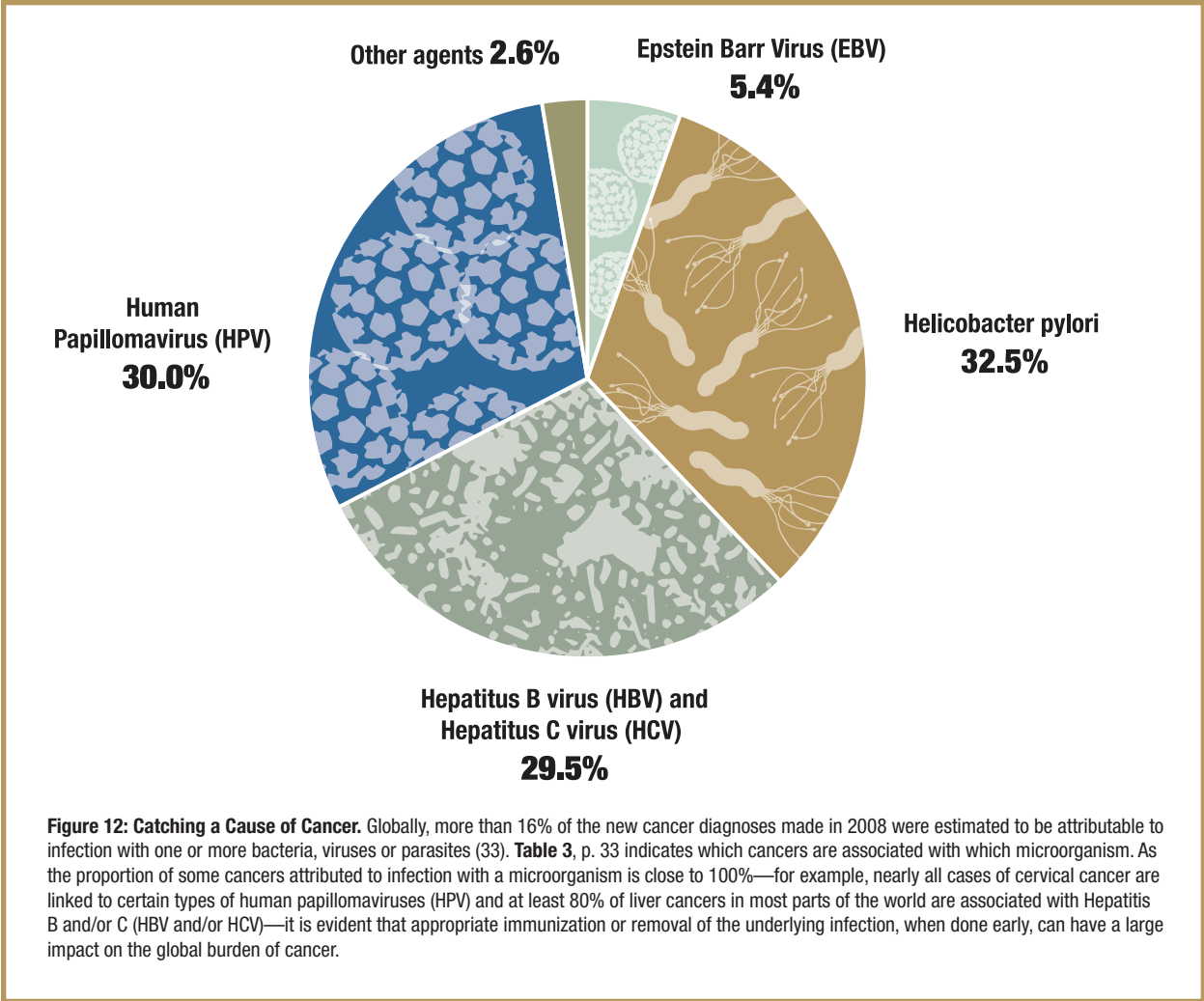
Increasing the price of tobacco products has been proven to reduce tobacco use, as indicated by the strong relationship between increases in cigarette prices in the U.S. from 1970 to 2007 and decreases in consumption (129, 130). This approach is particularly effective for children, who are two to three times more price sensitive than adults (131). In addition, it has been estimated that the April 2009 federal tobacco excise tax increase of 61 cents per pack reduced the number of smokers among middle and high school students in May 2009 by approximately 220,000–287,000 (132).

However, price increases alone will not stop all individuals from using tobacco products, and a comprehensive, evidence-based tobacco control policy employs price deterrents in combination with other proven measures in public education such as school-based programs or public advertising campaigns; federal, state, and regional regulations regarding the pricing or restricted sale or use of tobacco products; and clinical programs to provide the full range of cessation services or facilitate smokers' connections to public resources such as quitlines.



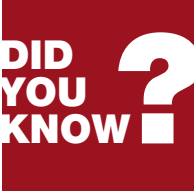
Smoking falls **2.5-5%** for every **10%** increase in the price of cigarettes.





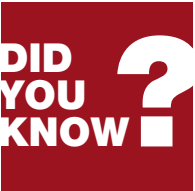
especially around midday; cover up with a shirt; wear a wide-brimmed hat; use sunglasses for eye protection; and apply a sunscreen rated SPF15 or higher at least every two hours. Adopting sun-safe habits is undoubtedly an important cancer prevention approach, as indicated by research showing that daily sunscreen use can cut the incidence of melanoma in half (26). However, more risk communication needs to be done to bring this to the attention of the general public.

The International Agency for Research on Cancer (IARC), an affiliate of the World Health Organization, includes UV tanning devices in its highest cancer-risk category, “carcinogenic to humans” (27), alongside agents such as plutonium, cigarettes and solar UV



that **ANYONE** can get skin cancer? However, non-Hispanic whites and men over 50 are at a higher risk of developing melanoma than the general population.

radiation. Avoiding the use of tanning beds and sunlamps would therefore decrease the incidence of skin cancer. However, tens of millions of Americans visit tanning salons each year (28). According to a 2011 report from the Centers for Disease Control and Prevention, this number includes more than 13% of all high school students and 21% of high school girls (29).



that sun bed use before the age of 35 **doubles** risk of melanoma?

Faced with the overwhelming scientific evidence that tanning bed use increases an individual’s risk for developing skin cancer and that the risk increases with younger age (30), some states, counties and cities in the U.S. have enacted legislation banning minors from using tanning beds. In other regions, however, similar initiatives have fallen short of approval (31).

**Table 3: 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, Hodgkin's and non-Hodgkin's 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

Preventing skin cancer by protecting skin from intense sun exposure and avoiding indoor tanning would not only limit the morbidity and mortality caused by these conditions, but would also save enormous amounts of money. For example, it has been estimated that the total direct cost associated with the treatment of melanoma in 2010 was \$2.36 billion in the U.S. (32). Given that melanoma incidence rates continue to increase (3), all sectors with a stake in reducing skin cancer burden—from patients, to researchers, to politicians seeking to balance their budgets—need to come together to develop and implement more effective policy changes and media campaigns.

**Infectious Agents: Catching a Cause of Cancer**

Research has revealed that infection with one of several microorganisms is an important cause of some cancers. The latest data indicate that worldwide, more than 16% of the new cancer



**Merkel cell carcinoma** is a rare but aggressive form of skin cancer, first described in 1972. Not until 2008, after considerable research efforts, was it discovered that a new human virus, Merkel cell polyomavirus, was found in about 80% of cases. Further research has determined that Merkel cell polyomavirus increases expression of a known cancer-promoting protein called surviving; thus, targeting this protein could provide a new approach to treating Merkel cell carcinoma.

diagnoses made in 2008, amounting to approximately 2 million affected individuals, were attributable to infections [(33); see Fig. 12, p. 32]. In the U.S. and other developed countries, this fraction was lower (7.4%) than in less-developed countries (22.9%). Several infection-associated cancers have high mortality rates, and preliminary estimates suggest that up to 20% of cancer deaths, or 1.5 million deaths, in 2008 were attributable to infections (33).

The International Agency for Research on Cancer lists 10 microorganisms in its highest cancer-risk category, “carcinogenic to humans” [(34); see Table 3]. These include the bacterium *Helicobacter pylori*; human papillomavirus (HPV); hepatitis B virus (HBV); hepatitis C virus (HCV); Epstein-Barr virus (EBV); human T cell lymphotropic virus type 1 (HTLV-1); human herpes virus type 8 (HHV-8; also known as Kaposi’s sarcoma herpes virus); the parasitic liver flukes *Opisthorchis viverrini* and *Clonorchis sinensis*; and the parasite *Schistosoma haematobium*. Recently, researchers have identified Merkel cell polyomavirus as the seventh virus directly linked to human cancers (35). Human immunodeficiency virus (HIV) is also associated with an increased risk for several types of cancer, but it is not considered carcinogenic because its effects are indirect—they are due to the effects of the virus on the immune system (see **Cancer-Predisposing Medical Conditions**, p.41).

The knowledge that infection with certain microorganisms can cause specific cancers has had a substantial effect on cancer prevention strategies. It has enabled the identification of individuals at elevated risk for developing cancer as well as the development of new methods for prevention and treatment. One of the best examples of how scientific discovery can lead to both of these key aspects of cancer prevention relates to HPV which is estimated to

“Thanks to prevention efforts and breakthroughs in cancer research, many more people are becoming cancer survivors rather than breast cancer victims.”

**Senator Dianne Feinstein (D-CA)**  
 Co-Chair of the Senate Cancer Coalition





have been responsible for almost 39,000 new cases of cancer in the U.S. in 2010 and more than 9,500 deaths (36).

As a result of several decades of research, we now know that persistent infection with certain strains of HPV can cause cervical cancer, a substantial proportion of anogenital cancers, and some head and neck cancers (33). This information led to the development of a clinical test that detects the presence of cancer-causing types of HPV. The test, when combined with a standard Papanicolaou (Pap) test for cervical cancer, enables earlier identification of women at high risk for cervical cancer and safely extends cervical cancer screening intervals (37).

Determining which strains of HPV can cause cervical cancer also fueled the development of vaccines to prevent persistent infection with these HPV types. The FDA has approved two vaccines for use in females aged nine to 25 years old for the prevention of cervical cancer caused by high-risk HPV strains. Both vaccines are highly effective at preventing precancerous cervical lesions caused by these HPV strains (36). The FDA also approved one of the vaccines, Gardasil, for use in females aged nine to 26 for the prevention of vulvar and vaginal precancerous lesions as well as in both males and females aged nine to 26 for the prevention of HPV-associated anal cancer (see **Sidebar on HPV Vaccine Usage**). Future studies will determine whether the vaccines also reduce the risk for head and neck cancers caused by HPV.

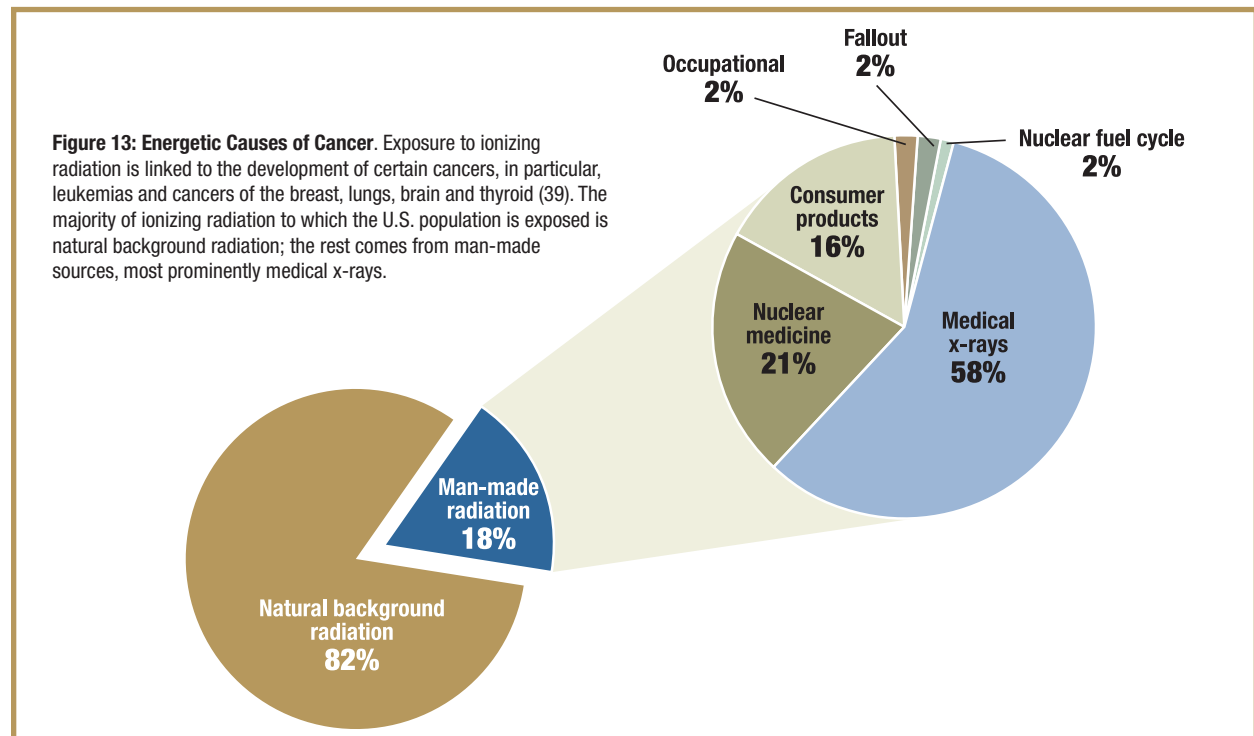
Our increasing knowledge about infectious causes of cancer provides opportunities for tremendous progress in reducing the health care and economic burden of certain cancers, like that

experienced by **Shaundra L. Hall**. Continued research in this area holds great promise for our conquest of certain cancers, but it will not have the desired effects without comprehensive approaches to public education and public health policy implementation—both of which are essential if cancer prevention advances are to be deployed to all those who could benefit.

## HPV Vaccine Usage

- Coverage for one dose of HPV vaccine for girls increased by only 4.4 percentage points to about 49 percent (48.7% in 2010 vs 44.3% in 2009).
- For girls who received the recommended three doses of HPV vaccine, coverage increased five points to just 32 percent (32% in 2010 vs. 26.7% in 2009).
- Of the girls who began the HPV vaccine series, 30% did not receive all three doses.
- Completion of the three-dose HPV series was lower among blacks and Hispanics than non-Hispanic whites
- Health insurance coverage for three doses of HPV vaccine was lower for those living below poverty.
- Poor and minority teens are less likely to receive all three recommended doses of the HPV vaccine.
- The CDC estimates that 1.4% of males age 13–17 years have received at least one dose of HPV vaccine.

Adapted from the CDC National Immunization Survey – 2010 Teen Survey available here: [http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6033a1.htm?s\\_cid=mm6033a1\\_w](http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6033a1.htm?s_cid=mm6033a1_w)





## Shaundra L. Hall

Age 42

Glendale, Ariz.

I am a 14-year cervical cancer survivor whose experience ignited a passion for educating the public—and parents in particular—about gynecological cancers and the fact that FDA-approved vaccines can now prevent many of these cancers.

In 1999, I was diagnosed with stage I squamous cell carcinoma of the cervix, when I was just 28 years old. My husband and I were trying to start a family, and after no success for about 10 months, I returned to my gynecologist for testing. I am very thankful that I did, because in the approximately 10 months since my previous clean Pap test, an aggressive tumor had grown on my cervix.

I had always been vigilant about having Pap tests each year, and for the prior four years, my results had been normal. Previously, I had had many years of abnormal Pap test results, leading to various procedures to remove affected cervical tissue, but I was still surprised to find out that I had developed invasive cancer. I now understand that I must have been suffering from persistent HPV infection for many years, even though there was not a lot of information published about the link between HPV and cervical cancer at that time.

Unlike several friends who had previously gone through cancer treatment, I did not have any chemotherapy or radiotherapy after my surgery. I really questioned that decision. However, my clinical team was confident that the surgical intervention was adequate, and now that I know more about chemotherapy, I recognize that it was the appropriate decision at that time. I did have follow-up Pap tests and scans every three months for a few years to check for any recurrence or metastasis, but now I am happy to say my only maintenance includes my yearly well-woman exam and Pap test.

Regrettably, I never received reproductive counseling. As a result, I was not aware until several years later that it would have been possible to have some of my eggs frozen, so that my husband and I could have had biological children with the help of a gestational carrier (surrogate). Even though the treatment left me unable to have children, I have been in remission for more than 14 years now and I am so thankful that I am able to live a very robust and fulfilling life.

Thanks to my status as a cancer survivor, I am able to act more effectively as a patient advocate. I volunteer for the National Cervical Cancer Coalition (NCCC) and use my cancer experience positively to educate people about gynecological cancers in particular. Cervical cancer, anal cancer, vulvar cancer and penile cancer are cancers that people do not particularly like to talk about, and it is important to let people know that these are not anything to be ashamed of. We are all in this together, as many of these cancers are often caused by HPV infection. My journey also led me to my career at Cancer Treatment Centers of America in Arizona, where I am fortunate to work and help others in their fights against cancer.

It is so vital that we educate the public about the FDA-approved HPV vaccines. This is one of my passions because it is critical parents understand the available information so they are able to make an educated decision along with their child's physician as to what the best course is for their child. I know that if I had children, I would absolutely have them vaccinated. I encourage any parent looking for more information regarding HPV or the FDA-approved vaccines to contact the NCCC ([www.nccc-online.org](http://www.nccc-online.org)) or the American Social Health Association ([www.ashastd.org](http://www.ashastd.org)).



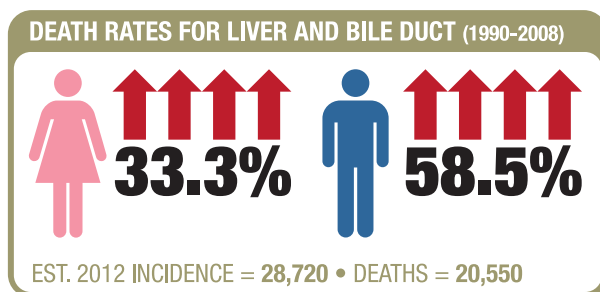


**DID YOU KNOW ?**

that at least **7** cancers have been linked to alcohol intake?

### ***Diet and Cancer: You Are What You Eat and Drink***

Dietary factors are important, but they do not appear to be uniformly relevant to all forms of cancer. The strongest scientific evidence is for alcohol intake, which has been linked to an increased risk for developing mouth, throat, larynx, esophagus, liver, colorectal and breast cancers (8). For each of these cancers, the risk increases with the amount of alcohol consumed, as highlighted by a recent study showing that even a few alcoholic drinks per week increase a woman's breast cancer risk (38). Developing and implementing more effective public health policies, media campaigns and education initiatives will be key to decreasing alcohol consumption, with the latter being particularly important given that almost 39% of high school students report current alcohol use (29).



For dietary factors other than alcohol, only limited research conducted thus far supports a direct link to cancer risk (8). Red meat and processed meat are both clearly associated with an increased risk for colorectal cancer, but for other cancers, their influence on risk is less certain scientifically. Moreover, no unequivocal evidence of preventive effects exists for any dietary factor, although some studies indicate the risk for some cancers is reduced through the consumption of fruits, vegetables and fiber.

The complexities of the relationship between food and nutrient intake and cancer risk are a key reason for the lack of a strong

evidence base in this area. Designing scientific studies to determine the contribution of a single dietary component is very challenging. Despite this, it is imperative that we continue to build upon our knowledge of the causes of cancer and increase the number of cancers that we can prevent through behavioral modifications such as consuming a healthy, balanced diet consisting of high amounts of fruit, non-starchy vegetables and fiber.

### **Causes of Cancer That Are Hard to Avoid**

We have discussed cancer risk factors that are possible to avoid, but there are other factors that are more difficult to elude.

### ***Ionizing Radiation: Energizing Cancer***

Extensive epidemiological and biological evidence links exposure to ionizing radiation with the development of cancer, in particular, leukemias and breast, lung, brain and thyroid cancers (39). Ionizing radiation is emitted from both natural and man-made sources (see **Fig. 13**, p. 34). In the U.S., 82% of annual exposure to ionizing radiation is composed of natural background radiation; the remaining 16% comes from man-made sources (39).

The main natural source of ionizing radiation is radon gas, which is released from the normal decay of certain components of rocks and soil. It usually exists at very low levels outdoors, but can accumulate to dangerous levels in areas without adequate ventilation, such as underground mines and home basements. Radon gas is the second leading cause of lung cancer after smoking and is responsible for between 15,000 and 22,000 deaths from lung cancer per year (40). This information led to policies for reducing exposure through home and business inspections and methods to contain or eliminate the source when possible. Increased awareness, along with further deployment of mitigation strategies, should further reduce the incidence of lung cancer caused by these exposures.

The predominant man-made source of ionizing radiation is medical equipment, treatments and diagnostic agents. Experts are concerned about the recent dramatic rise in the frequency of X-ray use for diagnostic purposes, such as CT scans (39). Thus, approaches are underway to limit radiation exposure from diagnostic CT scans with the use of new low-dose scanners. Also, educational programs have been launched to reduce the number of

“[This] is the time to reaffirm our further commitment to finding treatments, cures and better tools for prevention, building on the momentum of recent years. As the members of the American Association for Cancer Research and their partners continue their quest for cancer prevention and cures, Congress must stand behind them and invest in our research infrastructure.”

**Representative Lois Capps (D-CA-23rd)**

Co-Chair of the House Cancer Caucus



## Cancer Survivorship

According to the NCI, a cancer survivor is anyone living with, through or beyond a cancer diagnosis. Over the past several decades, tremendous advances have been made in the field of cancer research, and as a result, a large and growing community of cancer survivors now exists. For example, prior to 1970, being diagnosed with cancer during childhood was considered a universally fatal disease, whereas there are now approximately 300,000 survivors of pediatric cancer in the U.S., and the five-year survival rate is over 80%. Progress has been made against many other cancers as well, and the number of people living today with a history of cancer has risen to over 13.7 million — a significant increase from the 3 million survivors living in 1971(1).

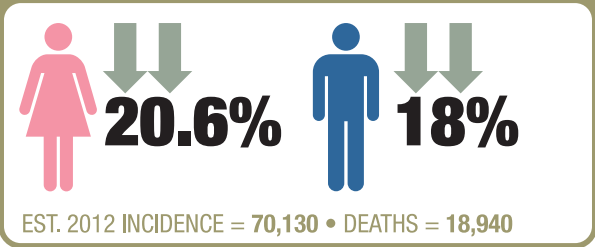
Long-term survivorship is also increasing: in the U.S. in 2012, an estimated 64% survivors were diagnosed with cancer five or more years ago and 15% were diagnosed 20 or more years ago. Nearly 50% of the current survivor population is 70 years of age or older, while only 5% are younger than 40. Earlier cancer detection and more effective treatments, along with the aging population, are expected to further increase the number of individuals living well beyond a cancer diagnosis.

While rising survivorship in and of itself is a sign of progress against cancer, survivors may suffer serious and persistent long-term adverse outcomes. Cancer survivors are at increased risk for and develop psychosocial and physiologic long-term and late effects of cancer treatment, including but not limited to: anxiety, depression, fear of cancer recurrence, damage to the heart, lung and kidney, cognitive impairment and infertility. Additionally, survivors are at risk for recurrence of the original cancer or the development of a new, biologically distinct, second primary cancer.

Adolescent and young adult oncology (AYA) survivors, age 15–39 years, along with pediatric cancer survivors, face a unique set of challenges compounded by their stage of life. For the AYA population, two out of every three childhood cancer survivors will develop at least one complication due to their prior therapy, and one out of every three will develop serious or life-threatening complications. Further, recent studies have concluded that AYA survivors are at higher risk for engaging in risky health behaviors known to increase cancer risk, such as smoking and drinking, which puts them at higher risk for developing additional cancers (133).

Following treatment, a person diagnosed with cancer may be faced with critical problems that diminish quality of life. The new research focus on cancer survivorship promises to play a significant role in the reduction of long-term and late effects. After decades of focus on cancer treatments and the attendant successes emerging from those efforts, researchers now face the challenge of helping the increased number of survivors achieve a higher quality of life by avoiding or diminishing the potential late adverse health consequences of successful therapies. By gaining a better understanding of the issues confronting cancer survivors, the cancer research community can continue to play an integral role in meeting the needs of survivors, their loved ones and future Americans diagnosed with this dreaded disease.

### DEATH RATES FOR NON-HODGKIN'S LYMPHOMA (1990-2008)



these procedures and to reduce radiation doses to what is medically essential.

Although high-dose radiation therapy is clearly beneficial for cancer treatment, patients are at increased risk for developing a second cancer, particularly pediatric patients. Given that the number of cancer survivors in the U.S. alone is now estimated at more than 13.7 million (3), this is a growing concern (see **Sidebar on Cancer Survivorship**). Research is needed to determine ways to identify those patients who are most sensitive to the negative health effects of radiation.

### **Environmental Pollutants: A Murky Link to Cancer**

The identification of environmental and workplace agents that cause cancer continues to be an important area of epidemiological and toxicological research. One of the most well-established links between an environmental pollutant and cancer is that between inhalation of asbestos and mesothelioma (41), an aggressive form of cancer for which new treatment options are urgently needed. The scientific determination of this causal relationship led to the use of preventive interventions and the implementation of important public health policies. However, asbestos remains a relevant risk factor today because it is still used in some commercial products within the U.S. In addition, not all the asbestos used in the last century has been removed. Moreover, erionite, a natural mineral fiber from volcanic ash that is similar to asbestos, is more potent than asbestos in causing mesothelioma and has been used in paving products in certain parts of the U.S. (42).

Many other environmental agents are classified as “likely to be cancer-causing” or “known to be carcinogenic” (41, 43). These agents include arsenic; pesticides; solvents used in the dry-cleaning industry and in paint thinners, paint and grease removers; dioxins, which are unwanted byproducts of chemical processes such as paper and pulp bleaching; polycyclic aromatic



not only does tobacco use cause cancer, but there is a **5% reduction** in the effectiveness of cancer treatment while smoking?

**Table 4: 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>

hydrocarbons, which primarily come from burning wood and fuel for homes but are also contained in gasoline and diesel exhaust; and metals like those contained in rechargeable batteries. Further study is required if we are to remain vigilant in our detection of cancer-causing agents in our environment and workplaces and to enhance our ability to determine who has been exposed.

**Hormones: A Natural Boost to Cancer**

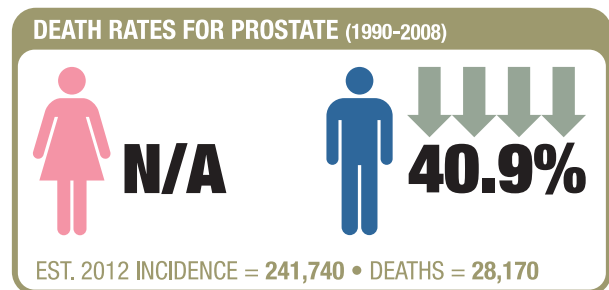
Scientific evidence has established that hormones modify a woman's risk for breast, ovarian and endometrial cancers. In particular, natural hormonal and reproductive factors that expose breast tissue to high levels of hormones for longer periods of time—beginning menstruation at an early age, experiencing menopause at a late age, first becoming pregnant at a late age and not having children at all—are linked to a small increase in breast cancer risk. Knowing these facts is a key component in determining a woman's likelihood for developing breast cancer.

In addition to the estrogen and progesterone produced by their own bodies, women are exposed to these hormones when they use oral

contraceptives (birth control pills) or medications to treat symptoms of menopause and other gynecological conditions. Epidemiological studies clearly indicate that oral contraceptive use decreases the risk for endometrial and ovarian cancer, and researchers have estimated that during the past 50 years, 200,000 cases of ovarian cancer and 100,000 deaths from the disease were prevented worldwide through the use of oral contraceptives (44).

The contribution of menopausal hormone therapy to cancer risk is an area of ongoing investigation. Several large epidemiological studies, including the Women's Health Initiative and the Million Women Study, revealed that therapies containing both estrogen and progestin, a synthetic form of the hormone progesterone, increase breast cancer risk in postmenopausal women who have a uterus (45, 46). Subsequent studies suggest, however, that the risk increase is not uniform for all women. More research is needed to clarify this issue.

The role of hormones in cancer causation is complicated further by environmental estrogens. Some epidemiological evidence indicates that plant-based, weak estrogens, such as those derived from soy products, may be beneficial, but only when consumed over a lifetime and perhaps only in Asian populations (47). Furthermore, new research is examining the influence of hormone-like substances in the environment, like those found in plastic containers and metal food cans. This emerging area of research illustrates the power of our biological and epidemiological knowledge of carcinogenesis in the evaluation of potential harm from modern-day products.





## How Do I know If I Am at Risk of Developing an Inherited Cancer?

If, in your family there is/are:

1. Many cases of an uncommon or rare type of cancer (like kidney cancer).
2. Members diagnosed with cancers at younger ages than usual (like colon cancer in a 20 year old).
3. One or more members that have more than one type of cancer (like a female relative with both breast and ovarian cancer).
4. One or more members with cancers in both of a pair of organs simultaneously (both eyes, both kidneys, both breasts).
5. More than one childhood cancer in siblings (like sarcoma in both a brother and a sister).
6. A close relative, like a parent or sibling, with cancer.
7. A history of a particular cancer among relatives on the same side of the family.

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

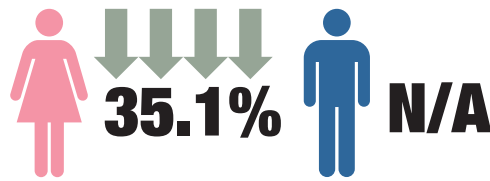
### Inheritable Causes of Cancer

#### *Inherited Risk: It's in Your Genes*

We now know that most, if not all, tumors arise from several genetic mutations that have accumulated in one cell of the body during the patient's lifetime. Unfortunately, in some families, several members can inherit a genetic mutation linked to cancer and have an increased risk for certain forms of the disease from birth. The NCI estimates that about 5% to 10% of all new cases of cancer in the U.S. each year, which is approximately 50,000 cases, are associated with an inherited mutation ((48); see **Table 4**, p. 38).

Retinoblastoma is one of the first cancers documented to be caused by an inherited, cancer-predisposing genetic mutation in some individuals (49). Retinoblastoma is a cancer of the eye that usually develops in early childhood, typically before the age of five. Although it is a rare cancer, diagnosed in just 250 to 350 children per year in the U.S. alone, analysis of retinoblastoma in the 1970s and 1980s revealed several of the tenets that underpin our current understanding of all cancers. For example, research demonstrated for the first time that mutations in a tumor suppressor gene, in this case the *RB1* gene, could initiate tumor formation. The important

#### DEATH RATES FOR CERVIX UTERI (1990-2008)



EST. 2012 INCIDENCE = 12,710 • DEATHS = 4,220

role that these findings played in advancing cancer research highlights the need to study all cancers, even those that affect very few people.

Cancers linked with inherited mutations in the tumor suppressor genes *BRCA1* and *BRCA2* are much more prevalent than those associated with *RB1* mutations. They constitute about 5% to 10% of breast cancer cases, such as **Melanie A. Nix's**, and 10% to 15% of ovarian cancer cases (50). A woman who has inherited a cancer-susceptibility mutation in one or both of these genes is about five times more likely to develop breast cancer and more than 10 times more likely to develop ovarian cancer compared with a woman who does not have such a mutation (51). Men who inherit these mutations are also at increased risk for developing breast cancer as well as pancreatic cancer and an aggressive form of prostate cancer.

Currently there is no way to correct inherited cancer-susceptibility mutations. However, the knowledge that an individual is in a high-risk category can encourage him/her to modify their behaviors to reduce risk from other factors, such as the use of tobacco and alcohol consumption; intensify participation in screening or early detection programs; or under certain circumstances, consider the options of taking a preventive medicine or having precautionary surgery to remove organs that are at greatest risk for cancer, as **Melanie A. Nix** did. At least some of these options are available to all patients who know they have a cancer-associated mutation, but additional research is needed to define the most comprehensive strategies for cancer risk reduction in different patient populations.

Despite clear advances in our understanding of inherited cancer risk, much remains to be learned. For example, although we know that a family history of cancer is a sign that a person may have inherited a cause of cancer (see **Sidebar on How Do I Know If I Am at Risk for Developing an Inherited Cancer?**), in most cases we do not know what the inherited genetic mutation is. Furthermore, we need to understand the genetic underpinnings of the inherited risk, which is one of many components contributing to



that having an affected first-degree relative (parent, sibling or child) roughly **doubles** an individual's risk of developing lung cancer?



## Melanie A. Nix

Age 42

University Park, Md.

I have been around breast cancer for most of my life. My mother was diagnosed with the disease when I was just eight years old. I also remember my grandmother being diagnosed with it when I was very young, and each of my three aunts has been affected by either breast cancer, ovarian cancer or both.

Given my family history, I knew I was at very high risk for developing breast cancer. After discussing this with my gynecologist in early 2008, he suggested that we needed to monitor my health much more aggressively and that I should begin by getting MRI screens rather than mammograms and by being tested for the *BRCA* gene mutations linked to breast and ovarian cancers.

I found out in July 2008 that I was *BRCA*-positive, with a mutation in my *BRCA1* gene that was most likely handed down to me from my mother. An MRI in November of that year revealed an area of concern, and a subsequent biopsy showed that I had stage I breast cancer. Further, it was triple-negative breast cancer, a very aggressive form of breast cancer that disproportionately affects African American women and younger women.

I was just 38, a wife and a mother of two young children. For the best chance of long-term, cancer-free survival, I decided to have a bilateral mastectomy, so that in addition to having my left breast with the cancer removed, I also had my right breast removed to reduce my risk for the disease emerging again in the future. Then, after 16 rounds of chemotherapy and breast reconstruction surgery, I had both my ovaries removed (a prophylactic bilateral oophorectomy) to further reduce my risks for cancer in the future.

I sometimes regret not having been tested for the *BRCA* gene mutations sooner, but there were a few things that held me back. Some of it was fear and anxiety about my future insurability, but much of it was that I was pretty sure that if I tested positive, I would be aggressive in my approach to preventing disease and would opt for a preventive bilateral mastectomy and oophorectomy. In preparing to have and breast-feed my second child, I held off getting tested.

My *BRCA* status is often at the forefront of my mind because I know that I am going to have to explain it to my children, in particular my daughter, when they get a little older. When the time comes, I will need to educate her about her cancer risks and how to monitor her own health. I will also have to teach her about her options for preventing the disease—whether or not to be tested for the mutation and what to do if she is positive.

I am very fortunate to be an almost four-year cancer survivor. Although I have not had any treatments since those I received right after my diagnosis, I will be under the care of an oncologist for the rest of my life. Right now, I see him every six months. In an effort to keep my risks for further cancer as low as possible and to contain any side effects of my treatments, such as osteoporosis, in addition to conscientiously going to my doctors' appointments, I exercise regularly, am very careful about my diet and take vitamin supplements.

As a result, I continue to thrive. I work with a childhood friend who was diagnosed with triple-negative breast cancer just before me to provide support and comfort for breast cancer patients who are going through treatment. I also volunteer with breast cancer advocacy and support organizations, because it is important that we raise awareness of this disease and the triple-negative form of it in particular. There is still so much to learn.





## Modeling Cancer Risk

For some cancers, researchers have used known risk factors to devise mathematical models that predict the likelihood that a person will develop these diseases. For example, the Gail and Claus models are used to determine a woman's risk of breast cancer.

Risk estimates derived using the Gail model are based on a woman's natural hormonal and reproductive history, family (first-degree relatives only) breast cancer history, race/ethnicity, breast biopsy history and the presence/absence of prior breast tissue abnormalities<sup>51</sup>. The Claus model considers only family history, but it incorporates maternal and paternal breast cancer history, first- and second-degree relatives and age of affected family members at breast cancer diagnosis. Each has its own strengths and limitations.

the differences in cancer incidence and mortality between racial and ethnic groups (see **Sidebar on Cancer Health Disparities in America**, p. 16). Defining the root causes of all cancers with an apparent inherited component, whether it is undiscovered genetic mutations or complex environmental and genetic interactions, is imperative if we are to break the cycle of disease for future generations.

### **Cancer-Predisposing Medical Conditions**

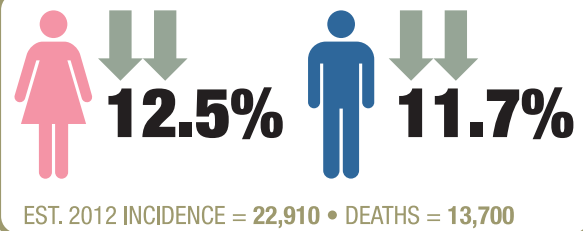
A number of medical conditions have been linked to an increased risk for certain types of cancer. Among these are the two major inflammatory bowel diseases, ulcerative colitis and Crohn's disease, and hereditary pancreatitis. Central to these conditions being cancer predisposing is the persistent inflammation that they cause. Patients with ulcerative colitis and Crohn's disease have inflammation of the lining of the colon, and they are six times more likely to develop colorectal cancer compared with the general population (52). The most effective strategy for reducing colorectal cancer risk in patients with inflammatory bowel disease remains unclear (52), and this is an area of active investigation. The options currently available include increased screening for early detection and precautionary surgery to remove all or part of the colon.

"For me, this is personal. I have lost two sisters to breast cancer, one brother to prostate cancer, and another brother to thyroid cancer. Tens of millions of Americans and their loved ones also have been touched by cancer. This is why I have long been an advocate of robust funding for cancer prevention and research."

**Senator Tom Harkin (D-IA)**



## DEATH RATES FOR BRAIN AND NERVOUS SYSTEM (1990-2008)

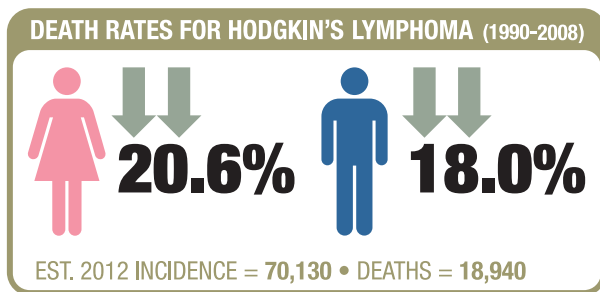


Research has shown that medical conditions that suppress the normal function of the immune system increase risk for certain types of cancer. For example, people with HIV/AIDS and patients taking immunosuppressive drugs after solid organ transplantation are more likely than healthy individuals to develop Hodgkin's lymphoma (53).

## Stratifying Risk to Improve Health Care for Everyone

Our increasing knowledge of risk factors for certain types of cancer provides unique prospects for reducing the burden of these intractable diseases by identifying those individuals at highest risk prior to disease onset and intervening earlier. For example, when this understanding is employed alongside our expanding awareness of the molecular profile of cancer development, specific prevention programs can be tailored to each high-risk patient's needs. It might be enough to assist patients in modifying their behaviors to reduce risk from other factors, such as tobacco use, or it might be necessary to increase their participation in screening or early detection programs or to recommend they consider taking a preventive medicine or having precautionary surgery to remove those organs at greatest risk for cancer.

Currently, there are few ways to reliably assess an individual's cancer risk without medical intervention. The most concrete approach is to classify as high-risk those individuals with an extensive family history of cancer and those with a cancer-predisposing medical condition (see **Sidebar on How Do I Know If I Am at Risk for Developing an Inherited Cancer?**, p. 39). Among the former, if it is suspected that disease in affected relatives could be caused by a known inherited cancer-susceptibility mutation, genetic testing can more specifically stratify each family member's



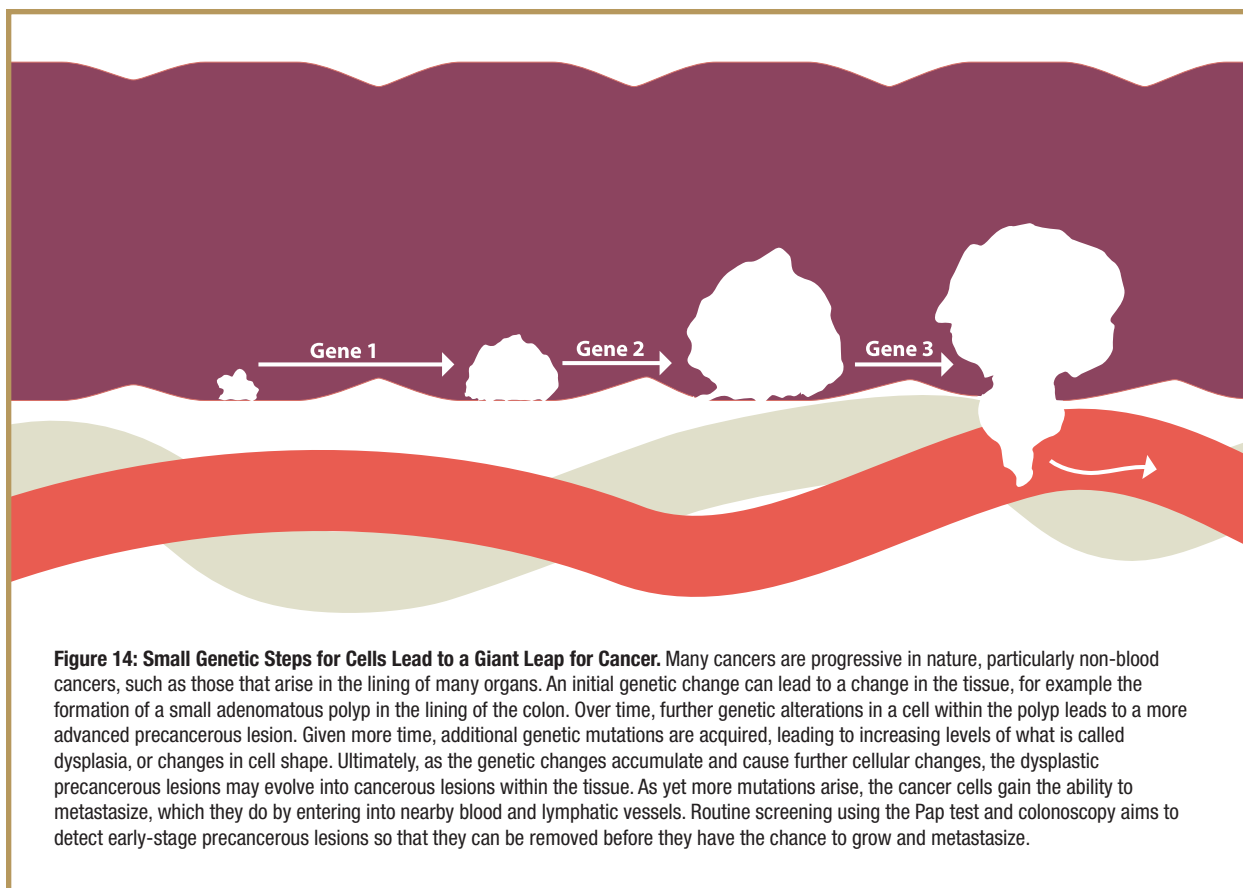
individual risk. In this way, relatives who carry the familial mutation can take appropriate risk-reducing measures, while those without the mutation can avoid unnecessary and costly medical procedures.

For the broader population, researchers have devised models to predict the likelihood that a person will develop certain cancers, with the goal of selecting those who may benefit from additional screening (see **Sidebar on Modeling Cancer Risk**, p. 41). These models are based on known risk factors, but are imperfect. The Gail and Claus models for determining a woman's risk for breast cancer are the most used commonly used in the clinic (54, 55). Further research to develop models that not only more accurately quantify risk, but also estimate the benefits of modifying risk factors (e.g.,

through eliminating tobacco use) is urgently needed if we are to target preventive interventions to the people who would benefit most.

Many researchers are seeking to identify biomarkers that could be used to stratify an individual's cancer risk—for example, biomarkers signifying exposure to a cancer-causing agent (see **Fig. 5**, p 23). Ideally these biomarkers would be measurable in small amounts of accessible material such as blood, urine or saliva. Current research in this area aims to harness recent technical advances and powerful analytical platforms to discover such biomarkers.

Clearly, stratifying risk is important for reducing the morbidity and mortality of cancer in high-risk individuals, but it also has the benefit of decreasing the complications and cost of unnecessary health care interventions for those at low risk for disease. Every medical procedure, even a seemingly harmless approach for screening for early detection of certain cancers, carries with it some risk for an adverse effect. Eliminating the need for low-risk individuals to be exposed to these procedures also reduces health care costs, providing additional impetus to expand our research efforts to develop new, accurate and reliable ways to discern an individual's cancer risk.



**Figure 14: Small Genetic Steps for Cells Lead to a Giant Leap for Cancer.** Many cancers are progressive in nature, particularly non-blood cancers, such as those that arise in the lining of many organs. An initial genetic change can lead to a change in the tissue, for example the formation of a small adenomatous polyp in the lining of the colon. Over time, further genetic alterations in a cell within the polyp leads to a more advanced precancerous lesion. Given more time, additional genetic mutations are acquired, leading to increasing levels of what is called dysplasia, or changes in cell shape. Ultimately, as the genetic changes accumulate and cause further cellular changes, the dysplastic precancerous lesions may evolve into cancerous lesions within the tissue. As yet more mutations arise, the cancer cells gain the ability to metastasize, which they do by entering into nearby blood and lymphatic vessels. Routine screening using the Pap test and colonoscopy aims to detect early-stage precancerous lesions so that they can be removed before they have the chance to grow and metastasize.

## Reducing Risk

### Screening to Spot Cancer Early

Finding a tumor early, before it has spread to other parts of the body, makes it more likely that the cancer can be treated successfully with fewer side effects and a better chance of survival.

Many cancers, particularly those that arise in tissues other than the blood, are progressive in nature. They begin with a series of genetic changes that translate into defined cellular changes that cause normal cells to develop into precancerous lesions, known as intraepithelial neoplasia (see **Fig. 14**, p. 42). As the genetic and cellular changes accumulate, the precancerous lesions may evolve into cancerous lesions contained within the tissue and ultimately into advanced metastatic disease. These processes typically take place over a period of many years, and improvements in our understanding of these changes and our ability to identify them have allowed us to detect some precancers and intercept them before they become advanced disease.

Population-based screening programs, which test generally healthy individuals for potential disease, provide opportunities to intervene in the cancer process as early as possible. For many years now, screening has been routinely conducted for the early detection of cervical cancer using the Pap test, for colon cancer using several approaches including colonoscopy, for breast cancer with mammography, and for prostate cancer using prostate-specific antigen (PSA) tests. Individuals at increased risk for cancers for which there are routine population-based screening programs are often advised to start screening at an earlier age or to be screened more frequently than those at average risk.

To be successful, a screening program must result in a decrease in the number of deaths from the screened cancer; all population-based screening programs are continually evaluated to ensure they



Cancer cells from a primary tumor, although extremely rare, can be found in the blood of patients with cancer. A team of researchers funded by Stand Up To Cancer is seeking to detect and analyze them to enable the detection of cancers.



There has been a **70%** decrease in cervical cancer deaths between 1955 and 1972, largely as a result of the Pap test.

meet this criterion. Effective screening programs must be well organized and must assess the majority of at-risk individuals. Screening for the early detection of cervical cancer using the Pap test is one of the best examples, as research has shown that reductions in cervical cancer incidence and mortality are proportional to the fraction of the population screened (56). In the U.S., widespread use of the Pap test contributed significantly to the almost 70% reduction in the number of deaths from cervical cancer between 1955 and 1972 (57) and has contributed to the further declines since then, particularly among African American women.

Colonoscopy has contributed significantly to the dramatic declines in colorectal cancer incidence seen since 1998 (58). However, only about 59% of Americans aged 50 years and older, the group for whom testing is currently recommended, get tested (59, 60). If the proportion of individuals following colorectal cancer screening guidelines increased to slightly more than 70%, researchers estimate that 1,000 additional lives per year could be saved (60). Clearly, innovative ways to increase the number of individuals following colorectal cancer screening guidelines are needed. The maximum impact is likely to be achieved with a diverse set of strategies, including public health and education initiatives and the development of alternative, less invasive screening strategies.

Regular screening for breast cancer with mammography is an effective, noninvasive way to detect the disease at an early stage, when treatment is more effective and a cure is more likely. Since the onset of regular mammography screening, the mortality rate from breast cancer has steadily decreased, and this has been attributed to both early detection through screening and improvements in treatment (3, 61). However, it is important to note that studies to date have not shown a benefit from regular screening mammography in women younger than the age 40. In addition, the use of routine mammography screening among those older than the age of 40 has become a hotly debated topic, because there is concern that it can detect breast tumors that will

“Awareness and access to screening are half the battle when it comes to battling breast cancer. It’s important to celebrate the advances we’ve made when it comes to detection and treatment.”

### Representative Sue Myrick (R-NC-9th)

Co-chair of the House Cancer Caucus and a breast cancer survivor





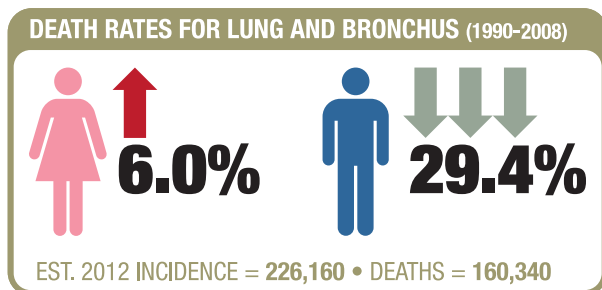


**1,000** more lives could be saved from colon cancer each year if 11% more of the population followed screening recommendations.

never cause symptoms or threaten a woman’s life. That is, it can potentially lead to overdiagnosis of the disease and subsequent overtreatment with its associated risks.

Almost 20 years after its introduction in the U.S., the use of the PSA test for early detection of prostate cancer is still controversial. The most recent analyses of two ongoing large-scale studies failed to conclusively indicate whether or not routine PSA screening is useful (62, 63). In one study, although annual PSA screening identified prostate cancers that would not otherwise have been detected, it did not reduce the number of prostate cancer deaths (62). In the other study, men undergoing a PSA screen once every four years had a 21% reduced risk for death from prostate cancer (63). Reconciling these data to generate guidelines for screening is difficult, and it is currently recommended that men, starting at age 50, talk to a doctor about the pros and cons of testing so they can decide if it is the right choice for them. Beyond the lack of clarity as to whether PSA screening saves lives from prostate cancer, screening may also lead to overdiagnosis and subsequent overtreatment, and therefore can cause harm.

The issue of overdiagnosis and overtreatment is relevant not only to mammography and PSA screening, but also to all approaches to early detection of cancer. Research to address the problem is vital to ensure that the public has confidence in current screening guidelines and any future changes in these guidelines. Moreover, it is evident that clinicians urgently need a way to distinguish among screen-positive patients—some may require treatment, while others can undergo surveillance and safely forego immediate curative interventions. One recent advance is the July 2012 FDA approval of the Prostate Health Index (*phi*), a blood test that can detect prostate cancer more accurately than the PSA test (64), thereby reducing the number of unnecessary medical procedures. This index can also help predict which prostate cancer patients need treatment (65). However, additional work is required if we are to comprehensively reduce the burden of overdiagnosis and



overtreatment while ensuring that those with significant disease are identified when curative treatment options are available.

For cancers other than cervical, colorectal, breast and prostate cancers, there are no routine screening strategies for individuals with an average risk for disease. Researchers have made some advances recently for early detection of lung cancer in current and former heavy smokers. In this population, researchers have reported that low-dose CT screening reduces lung cancer mortality by 20% because it identifies small tumors (66). However, this is an early result. More work is required to identify those current and former smokers at highest risk for developing lung cancer, because screening all of the estimated 94 million current and former smokers in the U.S. would be cost prohibitive.

Clearly, screening can greatly reduce cancer incidence and mortality in many instances. However, not all cancers are currently amenable to screening, and much research is needed to develop biomarkers to design new screening tools for cancers that we cannot currently detect until they reach an advanced stage, like pancreatic, liver and ovarian cancers. New imaging technologies also promise to provide new strategies for identifying premalignant lesions and early disease. As with all advances, the challenge will be to identify the populations that will benefit most and to determine the optimal frequency of screening. Cost containment to make approaches affordable will also be essential to success.

**Table 5: FDA-Approved Medicines for Cancer Risk Reduction or Treatment of Precancerous Conditions\***

Cancer Risk Reduction		
Condition	Generic Name	Trade Name
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 bivalent (types 16 and 18) vaccine	Cervarix
Treatment of Precancerous Conditions		
Condition	Generic Name	Trade Name
Actinic keratosis	ingenol mebutate	Picato
Actinic keratosis	fluorouracil	Adricil
Actinic keratosis	diclofenac sodium	Voltaren
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.

## Medical Interventions: Taking Action Early to Prevent the Onset of Cancer

Our increasing knowledge of the risk factors for and molecular drivers of certain cancers has enabled us to identify individuals with an extremely high risk for these diseases and to develop medical interventions to reduce these risks. Although having precautionary surgery to remove organs at greatest risk for cancer might seem drastic to most individuals, for women with an inherited *BRCA1* or *BRCA2* mutation who are known to have a markedly increased risk for breast cancer, it is a viable option. In these women, surgical removal of healthy breasts (a procedure known as bilateral prophylactic mastectomy) reduces breast cancer risk by more than 85% (67), while surgical removal of healthy fallopian tubes and ovaries (or prophylactic salpingo-oophorectomy) reduces ovarian/fallopian tube cancer risk by 80% and breast cancer risk by 50% (68).

Also, physicians can prescribe medications to some healthy individuals at high risk for cancer to reduce their risk (see **Table 5**, p. 44). The use of drugs for this purpose is known as chemoprevention. Scientific understanding that the hormone estrogen drives at least 65% of breast cancers led to the clinical deployment of two FDA-approved drugs that block the effects of estrogen, tamoxifen (Nolvadex) and raloxifene (Evista), as chemopreventive medicines for women at high risk for developing breast cancer. In such women, these drugs reduce the chance for developing breast cancer by about 50% (69, 70), but their use is not widespread, in part because tamoxifen increases risk for endometrial cancer and both agents may increase risk for blood clots and stroke. More recently, exemestane (Aromasin), which works by blocking the production of estrogen, has been shown to reduce the risk for invasive breast cancers by 65% in postmenopausal women at moderately increased risk, without significant side effects (71), providing an alternative way for some women to reduce their breast cancer risk.

Recognition that many cancers arise from precancerous lesions provides an opportunity for timely therapeutic intervention to prevent the development of invasive cancer. This is a very active area of research, and in January 2012, the FDA approved a new drug to treat precancerous skin lesions known as actinic keratoses (see **Table 1**, p. 14 and **Table 6**, Appendix). Actinic keratoses are rough, scaly patches on the skin that are considered precancerous because they can progress to squamous cell carcinoma, the second most common type of skin cancer. The new drug, ingenol mebutate (Picato), is a gel that patients apply once a day to the affected areas of skin. It clears these lesions in only three applications (72). This is a huge step forward for patients who previously had to undergo cryosurgery (the use of extreme cold to destroy the affected area) or who had to apply creams for several weeks or even months.



**33%** of cancer deaths are related to excess weight and physical inactivity.

Despite these successes, the use of medical interventions to reduce cancer risk is not widespread. Continued research is needed to develop better ways to identify at-risk patients, better screening approaches, and more and better ways to intervene earlier in the development of cancer.

# Making Research Count for Patients

Cancer research over the past four-plus decades 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. These advances have helped save millions of lives in the U.S. and worldwide.

This past progress has set us on our current path to a more complete understanding of cancer biology, which is moving cancer research in exciting new directions. Continued discovery is yielding further insights into the complexity of cancer, which exists at every level, from populations to individuals to specific cancers and to the very genes that drive these cancers. This unprecedented knowledge is beginning to transform the current standard of care, providing new hope for patients.

Uncovering the mysteries of cancer and translating them into breakthrough therapies for patient benefit requires the collaboration of researchers and physicians from various disciplines. In the past 12 months alone (September 2011 through the end of August 2012), the FDA approved eight new drugs for cancer treatment (see **Table 1**, p. 16), bringing to fruition the hard work of many thousands of individuals over many years. Also during this same period, the FDA approved additional uses for three existing drugs, increasing markedly the number of patients benefiting from them.

In the following discussion which focuses on these recent FDA approvals and also provides insight into other therapies that are showing near-term promise, it is important to note that these recently developed therapies are predominantly used in conjunction with the traditional triad of cancer patient care—surgery, radiotherapy and chemotherapy (see **Table 7**, Appendix). Although not highlighted in this report, substantial progress has been made

in these important areas of cancer medicine. Determining the optimal combination of treatment approaches is an area of intensive investigation.

## A New Day for Our Current Knowledge

The advanced technologies that researchers are using today to sequence cancer genomes, identify altered genes and proteins, and analyze the wealth of information from these technologies are making it increasingly possible to link specific defects in the molecular machinery of cells and tissues to cancer development. As a result, we now have the ability in some cases to identify the molecular drivers of an individual patient's tumor and use that information to select cancer therapies precisely targeted to the cancer-causing molecular deficiency. These therapies are more effective and less toxic than the treatments that have been the mainstay of patient care for decades, meaning that they are saving the lives of countless cancer patients as well as improving their quality of life.

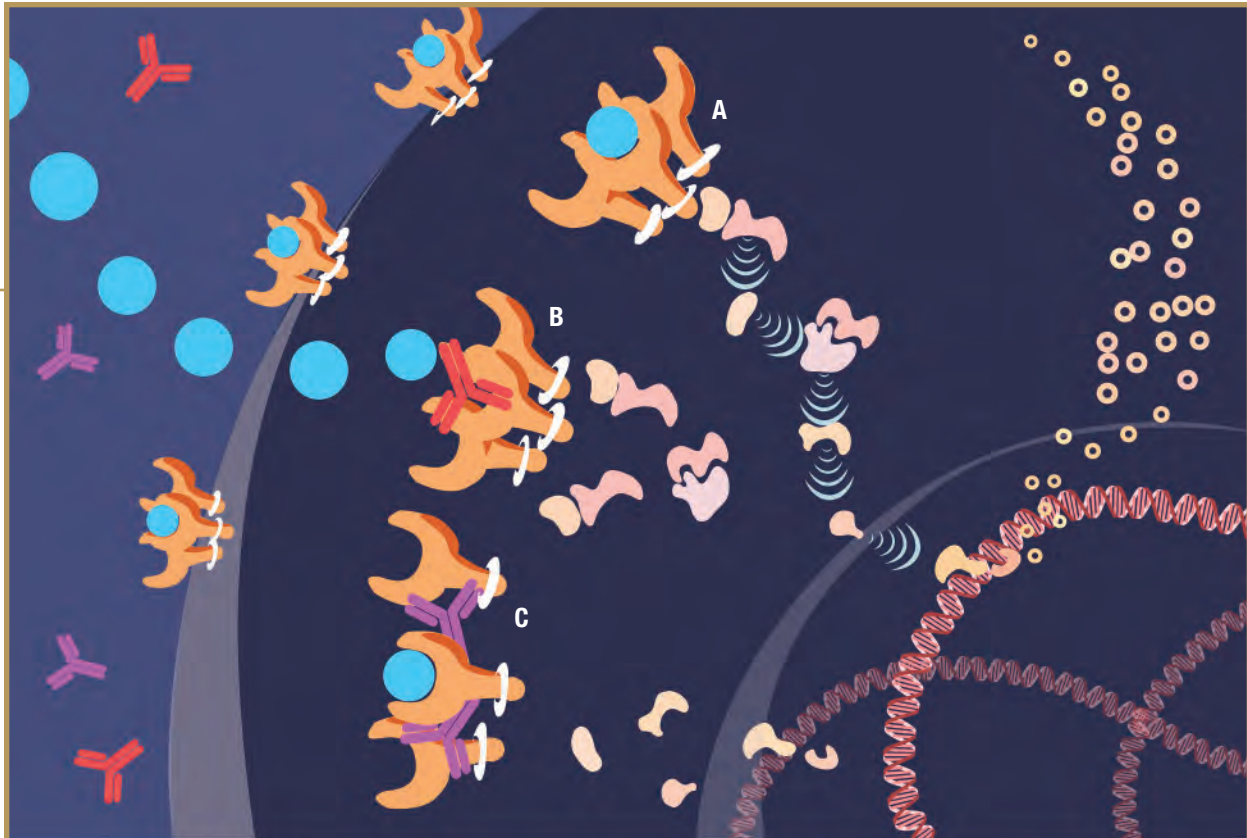
Despite the tremendous progress in patient care that has been achieved through the development and use of molecularly targeted drugs, at this time not all cancer patients are able to benefit to the same extent. In some individuals, a drug predicted to destroy the tumor fails to have any effect, and for others, the tumor responds initially but then starts to grow again. Other patients may have a tumor for which the specific underlying molecular defect has yet to be defined. Still other patients may have defined mutations that are not matched with a precisely targeted therapy. Leveraging our current knowledge has proven fruitful, both in enabling cancer researchers to address these challenges and in further advancing quality patient care.

“Our progress in fighting cancer since the National Cancer Act of 1971 has been nothing short of amazing.”

### Representative Rosa DeLauro (D-CT-3rd)

Former Chair and now Ranking Member on the House Appropriations Subcommittee on Labor-HHS-Ed, and an ovarian cancer survivor





**Figure 15: A New Drug, A New Approach to Stopping Breast Cancer.** Overactive HER2 signaling drives approximately 20% of breast cancers (A). In 1998, the FDA approved trastuzumab (Herceptin, orange therapeutic antibody in B), which blocks the blue growth factor from binding to the HER2 receptor found on the cell's surface; however, trastuzumab does not completely stop the HER2 signaling network (B). In 2012, the FDA approved pertuzumab (Perjeta, purple therapeutic antibody in C), which complements trastuzumab to more fully inhibit the HER2 signaling network (C).

## A New Day for Old Targets

Variability in patient responses to new target drugs is a major challenge in cancer treatment. While some patients' tumors will respond, some will not respond at all, and still others will initially respond and stabilize or begin to grow again. To meet this challenge, we need to understand what causes the variability and use this information to design combination therapies or new therapies to overcome these causes. This is an active area of research and it is beginning to bear fruit. In many cases, diligent analysis of the drug and its molecular target is critical, and it is enabling the design of more efficacious drugs that target the same molecule as the original therapies.

## Two New Ways to Hit a Breast Cancer Target

An estimated 226,870 new cases of breast cancer will be diagnosed in 2012 (3). In approximately one out of every five cases, the cancer overexpresses HER2 protein (73). These cancers tend to be aggressive and have a poor patient outlook. Decades of

fundamental research led to the clinical development and FDA approval of the therapeutic antibody trastuzumab (Herceptin), which exerts its anticancer effects after attaching to HER2 on the surface of the breast cancer cells. It revolutionized treatment for women with HER2-positive breast cancer, prolonging survival in those with metastatic disease by 24% (74) and reducing the risk of recurrence after surgery in those with early-stage disease by up to 24% (75). Unfortunately, some patients with advanced HER2-positive breast cancer fail to respond, and in most of those who do respond initially, the disease ultimately progresses. A second FDA-approved HER2-targeted therapy, lapatinib (Tykerb), provides some benefit in these situations (76, 77), but new therapies for this subtype of breast cancer are urgently needed.

Rigorous scientific assessment of the reasons why trastuzumab fails to eliminate all HER2-positive breast cancer cells in most patients led to the development of pertuzumab (Perjeta), which the FDA approved in June 2012 as part of a combination therapy for the treatment of metastatic HER2-positive breast cancer. The FDA-approved combination includes trastuzumab and pertuzumab



## Kathryn Becker

Age 46

Coconut Grove, Fla.

I am a 15-year breast cancer survivor. Although I didn't know it at diagnosis, because at that time no one knew about its important role in breast cancer, my cancer is HER2-positive. As a result, during the course of my many treatments, I've been able to benefit from all the research breakthroughs that led to the development of drugs that target HER2, like trastuzumab (Herceptin) and a new drug called T-DM1, which is only available through clinical trials.

My journey with cancer started in 1997. I had recently moved to Florida for my job, and I was doing the basic find-your-new-doctor thing, and I found a gynecologist. He found a lump, and said, "You need a mammogram." I was completely shocked and disoriented: I was too young to have cancer, no one in my family had cancer, and cancer wasn't even in my vocabulary.

I had the mammogram, which led to a biopsy, and then all of the sudden I had to make decisions like mastectomy or double mastectomy — things I'd never thought about. The hardest part for me was my age. I was 32, and thinking, "You want me to do what?" I chose to have a left mastectomy. After the surgery, I was still planning to have children, so I wanted to make sure I would be able to nurse someday.

Because I was young and I had an aggressive cancer my oncologist said, "If you're facing the enemy, do you want an Uzi or a pop gun?" Of course I chose the Uzi. So we went down the path of high-dose chemotherapy with stem cell recovery. It pushed me into menopause, so children were out of the question. That wasn't part of the literature I received. A nurse pulled me aside and said, "You know this will make you sterile." I had no idea. But on the other hand, I really believe that having undergone that treatment helped hold off my cancer recurrence.

I did not have a recurrence until 2004. The cancer returned with a vengeance in my liver, lungs, ribs and sternum. I went to Memorial Sloan-Kettering in New York for a second opinion, but the oncologist there was on the same page as my oncologist in Florida, so I decided to stay at Advanced Medical Specialties in Miami for more chemotherapy. I lost my toenails and fingernails; it was gross. Afterwards, I still had some cancer in my bones, but the rest was gone. Since then, there have only been short periods of time that I haven't been on treatment. We'll get tumors to shrink so they are really small and then something will grow. We've been going through this process for a while now.

In October 2010, I started traveling to Fort Lauderdale to take T-DM1 as part of a clinical trial. At first, I had a really good response. The swelling and tenderness on my sternum really started to diminish. It was the first time I had ever felt my cancer get better. It was pretty quick with T-DM1. But in January 2012, my scans revealed that I had a little more growth on my sternum and some more lymph nodes involved. I've been off the trial for about six months. I'm on another drug now, so we're seeing how that goes.

While I was participating in the T-DM1 trial, I saw many women around me go into remission. I hadn't been around that before and it was exciting. All these women were doing well; the ones who weren't were women like me, the ones with cancer in their bones. I loved seeing all those women go into remission. The drug is completely tolerable, and the quality of life is night and day from the "Uzi" drugs I took more than 10 years ago. These drugs are the sharpshooters. I've lost quite a few friends to cancer over the years, and I wish they had been able to have some of these drugs because then they'd probably still be around now.

Is this disease curable one day? I think so. Do I have a really aggressive cancer? Yes, but through Susan G. Komen for the Cure, I've been able to meet other metastatic breast cancer survivors, and although there aren't a lot of us, it's becoming clear that there is a future for us.







**Antibodies** are natural proteins made by a type of immune cell, called a B cell. Researchers have developed ways to generate antibodies that can be used to treat cancer alone or by attaching chemotherapy drugs or radiation-emitting particles to them in order to deliver these directly to the cancer cells.

because together, they are thought to provide a far more comprehensive blockade of HER2 function, and thus greater anticancer activity than either does alone (see **Fig. 15**, p. 47). In patients with advanced HER2-positive breast cancer, this dual targeting of a single molecule (HER2) significantly prolongs the time to disease progression by almost 50% (73).

An exciting new approach to treating women with HER2-positive breast cancer is currently in the early stages of clinical testing. The drug being studied, called T-DM1, is an antibody-drug conjugate, and its development is the culmination of many years of dedicated collaboration among researchers from many different disciplines. Antibody-drug conjugates are a new type of targeted therapy that uses an antibody component to deliver cytotoxic chemotherapy drugs more precisely to just those cancer cells that express the antibody target. This precision reduces the side effects of the chemotherapy agent compared with systemic delivery. In the case of T-DM1, a small amount of the chemotherapy drug DM1 is attached to trastuzumab, which delivers the DM1 directly to HER2-positive cancer cells. Early results from clinical trials of T-DM1, suggest that the drug significantly reduces the risk of cancer progression or death in many women who, like **Kathryn Becker**, have metastatic HER2-positive breast cancer (78). Additional time to follow the patients on these trials is needed to make a definitive conclusion as to the efficacy of this approach.

### **What to Do When One of the Most Effective Molecularly Targeted Drugs Doesn't Work**

Imatinib (Gleevec) was the first molecularly targeted chemical developed for cancer treatment. Its discovery was the result of a series of groundbreaking scientific findings. First, chronic myelogenous leukemia (CML) was linked to an abnormal chromosome in tumor cells, called the Philadelphia chromosome; subsequently, researchers found that two genes, *BCR* and *ABL*, were fused to create both the odd chromosome and a mutated protein that fueled this cancer type. Because imatinib effectively blocks the activity of the BCR-ABL fusion protein, its 2001 FDA approval changed the lives of CML patients. Five-year survival rates increased from just 31% to more than 90% (3, 79). Unfortunately, a small fraction of patients fail to respond to imatinib. Other patients initially respond, but eventually stop. In these cases, when the disease returns, or relapses, the leukemia is said to have acquired resistance to imatinib (see **Sidebar on Drug Resistance and Fig. 16**, p. 50).

## Drug Resistance

Drug resistance is one of the greatest challenges we face today in cancer treatment. Most tumors that are not completely eliminated will, over time, become resistant to a given therapy and continue to progress.

Resistance generally falls into two categories: acquired resistance, which develops during the course of treatment in response to the therapy; and innate resistance, which is inherent at the outset of treatment.

Diversity among the cancer cells within a single tumor is what ultimately drives insensitivity to treatment with cytotoxic and molecularly based therapeutics alike. For example, within a given cancer, some cells may be actively proliferating, while others are not. Since many cytotoxic therapies destroy only rapidly dividing cells, some cells within a cancer escape these treatments. In addition, the unstable and error-prone genome in a cancer may create a mutation in the drug target itself, rendering the drug useless in a subpopulation of cells.

Redundancies within the signaling networks that drive cancer cell proliferation also can permit cells to become resistant to therapy. In this case, an initial therapeutic can block a signaling pathway within a network, but given the pressure to continue proliferating, the cell can use a “detour” around the blockade and continue through the network.

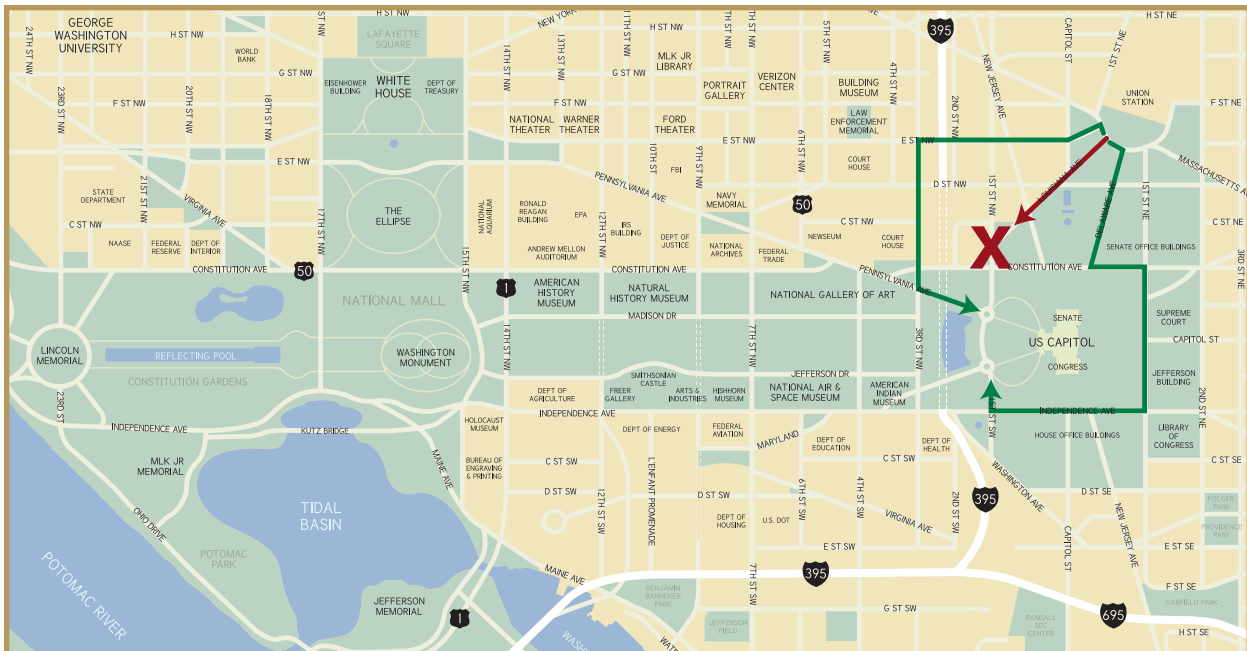
Molecular classification enables physicians to treat cancer patients with the most effective therapy for their tumor type, an advance that is now improving the lives of countless cancer patients; however, some patients, despite having the correct molecular defect, do not initially respond to the therapy, which is called innate or primary resistance. This may be because of genetic mutations present in the tumor itself, or it could be because of a genetic variation within the patient that alters drug activity or metabolism, or a combination of the two.

In order to develop therapies that will overcome drug resistance, we need to continue to make inroads in understanding the ways in which cancers develop drug resistance, as well as the factors within the tumor and the patient that drive innate resistance. This will only be possible with a continued investment in the research to do so.

### DEATH RATES FOR ORAL CAVITY AND PHARYNX (1990-2008)



EST. 2012 INCIDENCE = 40,250 • DEATHS = 7,850



**Figure 16: Many Avenues To Navigate Around a Drug.** Signaling networks within a cell resemble a grid of streets in a city, and drugs attempt to stop these signals like a roadblock stops traffic. Much like gridlocked traffic, cancer cells can take advantage of alternative routes by using overlapping or parallel pathways to continue transmitting signals in spite of the drug's blockade. This helps explain why some drugs that block key nodes of signaling networks are initially effective at stopping cancer growth, but stop working when alternative "routes" start to be used, leading to a form of drug resistance. Imagine the streets of downtown Washington, D.C.: if a roadblock (red X) was placed at 1st and Constitution, traffic would be temporarily blocked from reaching the Capitol (red arrow), but eventually traffic would find alternative routes (green arrows). So it is with targeted therapeutics. For some cancers, research has already identified the alternative routes that are used, and combinations of drugs that block both the main and alternative pathways simultaneously are currently in clinical testing. For others, more work is required to identify the alternative paths and the drugs that may block them.

Fundamental research determined that those patients who either fail to respond or ultimately relapse have leukemias that harbor mutations in imatinib's target, the BCR-ABL fusion protein, that prevent the drug from blocking BCR-ABL activity. Researchers have identified ways to circumvent most of these mutations, and two second-generation drugs, dasatinib (Sprycel) and nilotinib (Tasigna), were developed and FDA approved. However, both fail to block one particular mutation, and that remains a significant clinical problem. Fortunately, recent advances have led to the development of an investigational drug, ponatinib, which is active against this mutation. Ponatinib is showing tremendous promise in phase II clinical trials, where robust anti-leukemic activity has been reported in patients with CML that is resistant or intolerant to currently available treatments.

### **Refining Drug Potency and Specificity**

The striking success of drugs such as imatinib is very encouraging in that they precisely target the cancer-driving molecular aberrations that are intrinsic to cancer cells. However, recent clinical experience has revealed that for many cancers, in particular those affecting large organs such as the liver and kidneys, targeting cancer cells alone is not sufficient to completely treat a patient's cancer. In the case of the most common type of kidney cancer in

adults, which is renal cell carcinoma, research has identified that these cancers are particularly dependent on the growth of new blood and lymphatic vessels to grow and thrive. Thus, they are the perfect targets for therapeutic intervention.

Over the past decade, the FDA has approved seven drugs that work in similar ways to impede the growth and stability of the emerging blood and lymphatic vessel networks. These drugs target a family of growth molecules and their receptors, called VEGF, which are found mostly on blood and lymphatic vessel walls. These therapies have significantly improved outcomes in patients with metastatic renal cell carcinoma, a particularly insidious stage of the disease that is resistant to conventional chemo- and radiotherapy, and which has a five-year survival rate of less than 10% (80). Of the antiangiogenesis drugs that block the VEGF receptors, their ability to suspend new vessel growth differs, due in part to varying



**Cytotoxic chemotherapy drugs** largely work by non-specifically eliminating all rapidly dividing cells. They can therefore cause damage to those normal cells that are rapidly dividing.



## The University of Texas MD Anderson Cancer Center Houston, Texas

- Is the only NCI-designated comprehensive cancer center in Texas.
- Employs 18,456 people.
- Admitted 1,190,568 outpatients and 25,230 inpatients in fiscal year 2011.

Source: MD Anderson Annual Report 2010-2011

Knowledge gained through research discoveries at The University of Texas MD Anderson Cancer Center has an impact on the U.S. economy of:

- \$20.1 billion in annual spending
- \$9.8 billion in annual output
- More than 112,500 permanent jobs

Source: Figures from The Perryman Group, a Texas-based economic and financial analysis firm 2009  
<http://www.mdanderson.org/about-us/facts-and-history/economic-impact/index.html>

efficiency in VEGF blockade as well as their effects on several related molecules. Drugs with greater potency and specificity for the VEGF receptors are being developed; for example, the FDA approved a new drug in this class, axitinib (Inlyta), for the treatment of renal cell carcinoma in January 2012 (81). Furthermore, in August 2012, the FDA approved the newest member of this growing family, ziv-aflibercept (Zaltrap), for the treatment of metastatic colorectal cancer.

Drugs that block the VEGF receptors, disrupting the blood and lymphatic vessel networks that grow to support a cancer's growth, are not just used to combat renal cell carcinoma; they are also FDA approved for the treatment of the most aggressive form of liver cancer, some forms of pancreatic cancer, and some lung and colorectal cancers. An emerging new drug in this class of therapies is regorafenib, which potently targets the TIE2 receptor in addition to the VEGF receptors. This agent has the potential to increase its effectiveness as a therapy, since TIE2 is also believed to play an important role in blood and lymphatic vessel stability and growth. Regorafenib is currently being tested in clinical trials as a treatment for several advanced stage cancers. Particularly promising are the preliminary results of a large study examining its utility as a treatment for patients with metastatic colorectal cancer (82). With a five-year survival rate of only 12% with this disease, there is a huge need for new treatment options (3). See **the female metastatic colorectal cancer survivor's story**.

### **Improving Patient Quality of Life by Reducing Side Effects**

The FDA approved bortezomib (Velcade) for the treatment of multiple myeloma in 2003 and for the treatment of one of the rarest but fastest growing forms of non-Hodgkin's lymphoma,

## Female with metastatic colorectal cancer

Age 48, Indiana

I was nearly 45 years old when I was diagnosed with stage IV metastatic colorectal cancer. I have just started on the second cycle of what is currently the only treatment option left for me, a drug called regorafenib, which I am receiving through an expanded access program that is available while the FDA considers whether or not to approve it. I am trying to be positive. My doctors told me that someone has to be at the top end of the spectrum of responses, and we are hoping that is me.

My journey to diagnosis started with routine blood tests that showed I was slightly anemic. I had never been anemic in my life, so my doctor ordered a range of tests. A colonoscopy revealed the answer. It was a huge shock. I had no symptoms—how could I possibly have advanced cancer?

After the colonoscopy everything moved very quickly, and I found myself in surgery just 10 days later. Slight complications from the surgery meant that I did not start my chemotherapy until five weeks later. After 11 rounds of bevacizumab (Avastin) and a combination of chemotherapy drugs called FOLFOX, I had a CT scan and a PET scan. The results looked good, so I stopped that treatment and went onto a maintenance chemotherapy protocol that comprised bevacizumab and two chemotherapy drugs, 5-FU and leucovorin. After five months, in May 2010, I came off all treatments.

My next CT scan, just a few months later, in July 2010, revealed cancer spots in my liver, and I was treated with stereotactic radiation. Three months later, I had my next CT scan. The results were not good. There were more areas of cancer, and I had to go back on chemotherapy. This time, I participated in a clinical trial that was testing the effectiveness of the drug everolimus (Afinitor), in combination with cetuximab (Erbix) and irinotecan, in patients with metastatic colorectal cancer. I came off it after five months because it was not working—my cancer kept progressing—and the side effects were truly, truly awful.

By then it was March 2011. I went back onto bevacizumab, but this time I took it in combination with the chemotherapy drugs oxaliplatin and capecitabine (Xeloda). My oncologist and I decided to just keep on going with this treatment because we knew there were no others, and I was not prepared to enroll in another clinical trial after my horrendous experience with everolimus. The only reason I stopped taking these drugs, in early 2012, was because my insurance company insisted that I did. They stipulated that the only treatment they would pay for was irinotecan, despite the fact that it had not benefited me when I took it previously.

At this point, I sought another opinion. I went to The University of Texas MD Anderson Cancer Center, and there they told me that yes, my only option was to take the irinotecan. But they also said that if I did this for three months and my cancer continued to progress, then I should be able to get into the regorafenib expanded access program that would likely be opening up at that time.

So that is what I did, and my cancer progressed, and in June 2012, I started my first cycle of regorafenib. Fortunately, the side effects of regorafenib are nowhere near as severe as those of everolimus, they are not pleasant, but they are not unbearable. I can tell I will be able to keep taking it for as long as it is benefiting me. My first scans after starting the drug are in August 2012, and I'm keeping my fingers crossed because this really is my last shot.

*Just before printing, we learned that this patient is no longer taking regorafenib, because her disease has progressed. Although regorafenib has benefited other patients, this failure highlights the challenge of treating metastatic disease for many, if not all cancers.*





## Congressman M. Robert Carr

Age 69

Washington, D.C.

My cancer showed a complete response to treatment and has been undetectable since 2008. I am keenly aware that my status as a cancer survivor owes much not only to my personal doctors, but also to all those researchers and patients whose catalogued, cumulative experience contributed to my successful treatment. I am especially grateful to those patients whose treatment was not successful, but whose legacy was in the lessons learned by the professionals who advanced, no matter how small, the knowledge necessary to succeed and to save lives like mine.

I received my diagnosis of multiple myeloma in 2007, just two weeks before I was due to run my second Marine Corps marathon. I was lucky; it was later determined that my disease was extensive and accompanied by kidney problems. My doctors told me that if I had run that marathon, my outcome might not have been as good as it has been.

I started treatment the day I found out that 85% of the cells in my bone marrow biopsy were cancerous plasma cells, which meant that I had stage III disease. Luck was with me again at this point because the drug I was given, bortezomib (Velcade), had only been FDA approved for my condition a few weeks earlier. I was given bortezomib for 23 weeks, and each time I had a shot I had to take a high dose of steroids for two days.

The only side effect I experienced from the bortezomib was neuropathy in my feet, although that was bad enough. The steroids, however, were incredibly hard to endure; they gave me huge ups and downs—I would feel great the days I took them and then absolutely awful after that. I was very glad to be done after 23 weeks, at which point fewer than 3% of the cells in my bone marrow biopsy were cancerous.

Although my response to the bortezomib and steroids was very good, and my doctor says it saved my kidneys, I did have to undergo a stem cell transplant to get rid of the remaining cancer cells. The high-dose chemotherapy that preceded the transplant was agonizing, and the whole process took almost a year. But I am thankful. I have been in remission since the stem cell transplant, and I live a normal life. I take lenalidomide to keep the cancer at bay and my blood is checked every 30 to 45 days, but I just live with that. Running a marathon or a 10K is much more arduous, and something I do regularly.

My cancer experience taught me not to take health and health care for granted. I was lucky enough to be treated by a doctor who is one of the most knowledgeable about multiple myeloma and to have health care that enabled me to receive state-of-the-art treatment. But I have a nagging guilt because there are people with the same disease as me who could be treated successfully if they could just get access to the right treatments. I very much hope that in the future, I will get a chance to make a difference and help open up access to health care.

mantle cell lymphoma, in 2006. The drug is highly effective in patients with multiple myeloma, with its use almost doubling the five-year survival rate. Many patients, like **Congressman M. Robert Carr**, have achieved a durable complete response to the treatment (83).

Bortezomib is a unique drug that blocks the breakdown of proteins, leading to the disruption of multiple pathways that are necessary for tumor cell proliferation. Its mode of action is not as precise as that of drugs that target cancer-driving molecular defects intrinsic to cancer cells, and as a result it has significant side effects. One side effect that considerably diminishes the quality of life of many patients is a condition called peripheral neuropathy, which causes numbness, loss of sensation and pain in the hands and feet.

Two FDA decisions in 2012 should help reduce this serious adverse side effect and will increase the number of treatment options available to patients with multiple myeloma. The first is the July 2012 FDA approval of carfilzomib (Kyprolis) as a new treatment for multiple myeloma. Like bortezomib, carfilzomib prevents the breakdown of proteins, but its blocking effects are more sustained and it can be administered on a schedule that is effective but significantly reduces peripheral neuropathy (84). The second is the January 2012 FDA approval of a change to the way that bortezomib can be given to patients. Clinical trial results indicated that administering bortezomib under the skin, rather than into the veins, did not diminish treatment effectiveness, but dramatically reduced suffering related to severe peripheral neuropathy (85).

### A New Day for Existing Drugs

After performing arduous clinical trials that lead to FDA approval for a drug, researchers and clinicians continue their endeavors, seeking to maximize the number of patients who can benefit. Determining if treatments for certain cancers might benefit other groups of patients and if a drug's side effects can be mitigated to make it tolerable to more people not only improves patient care, but it also increases the return on prior investments in cancer research. In the first eight months of 2012, the FDA expanded the use of three previously approved cancer treatments—pazopanib (Votrient), everolimus (Afinitor) and, as noted above, bortezomib—increasing their true clinical worth.



#### MedStar Washington Hospital Center Washington, DC.

- Employs approximately 6,100 associates.
- Admitted 40,192 inpatients, 2,062 of which were cancer-related admissions in 2011.
- Admitted 411,514 outpatients, 82,190 of which were cancer-related admission in 2011.



#### Dana-Farber Cancer Institute Boston, Mass.

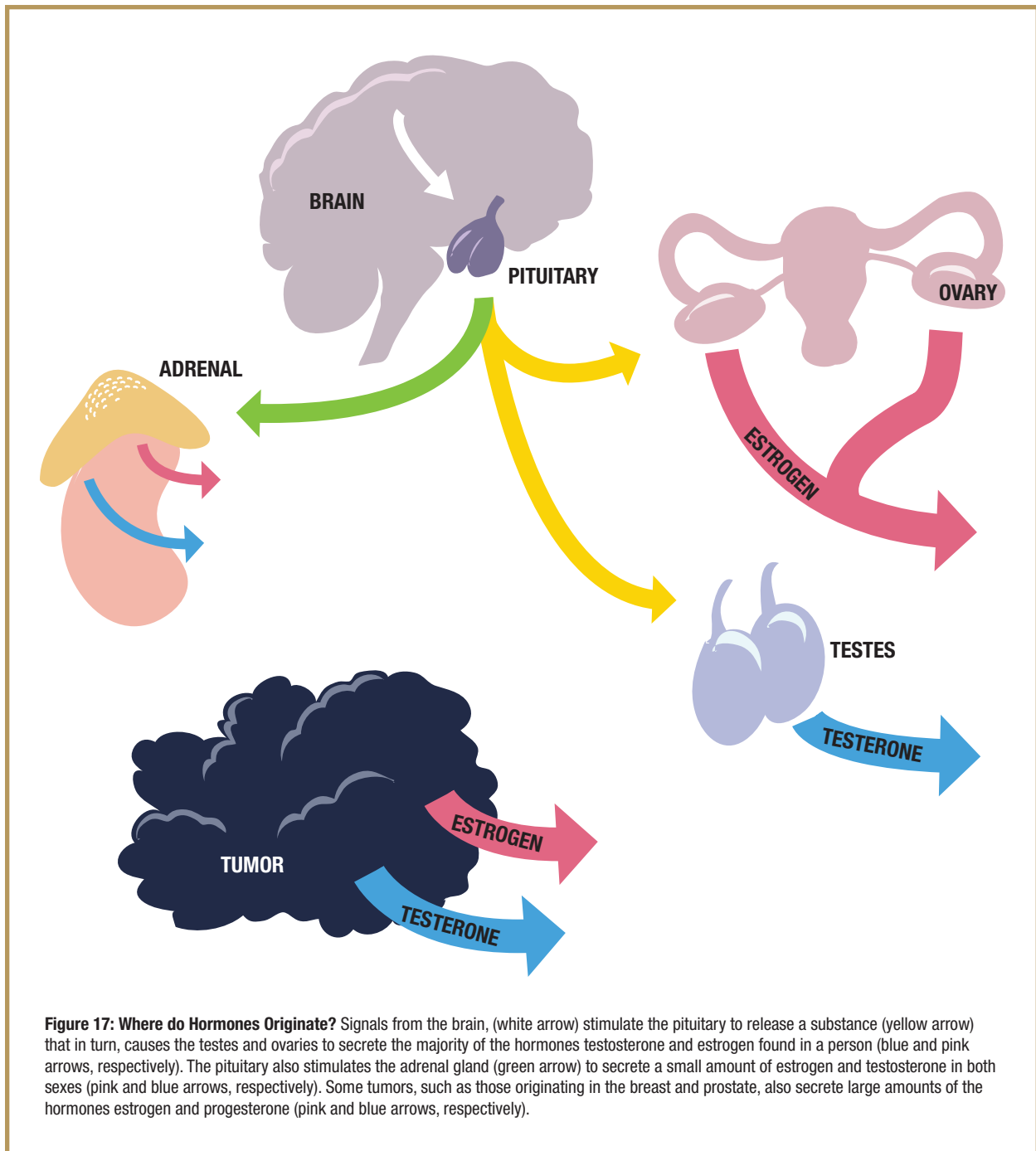
- Is the only NCI-designated comprehensive cancer center in Massachusetts.
- Employs 3,763 people.
- Had more than 353,000 adult and pediatric outpatient clinic visits and infusions in 2011.

The FDA approved pazopanib for the treatment of metastatic renal cell carcinoma in October 2009. It targets the VEGF receptor family, disrupting the growth and stability of the emerging blood and lymphatic vessel networks that support the cancer's growth. A recent large-scale clinical trial showed that pazopanib more than doubles the time to disease progression in patients with certain metastatic soft-tissue sarcomas (86), a group of cancers that it is estimated will be newly diagnosed in more than 11,000 Americans in 2012 (3). In light of this, in April 2012, the FDA approved the drug as a treatment for advanced soft tissue sarcoma, providing new hope for patients who have seen little change in their treatment options for decades.

Everolimus targets the key molecule, mTOR, in the mTOR signaling pathway, which senses energy levels, controls tumor cell viability and drives cell growth. As a result of various genetic mutations, this pathway is overactive in several types of cancer, and over the past few years the FDA has approved everolimus for the treatment of metastatic renal cell carcinoma, certain pancreatic cancers called neuroendocrine tumors, and noncancerous brain tumors in patients with an incurable inherited disease called tuberous sclerosis (see **Table 4**, p. 38). Between 25,000 and 40,000 Americans have tuberous sclerosis, which causes noncancerous tumors to grow in the brain and many other vital organs (87). A recent clinical study indicated that everolimus reduces the burden of noncancerous brain tumors in patients with tuberous sclerosis and also dramatically shrinks their noncancerous kidney tumors, data that led to the April 2012 FDA approval of everolimus for this condition (88). In July 2012, the FDA approved everolimus for the treatment of women with hormone receptor–positive advanced breast cancer (see below) after a large-scale trial showed it significantly prolonged time to disease progression or death (89).

Increasing the number of cancer types for which a drug is approved as a treatment is not a trivial advance. It is one that is significant for the many patients, their families and their loved ones who have benefitted from this progress. Numerous studies are underway to pair other proven cancer treatments with new patient populations, and these are expected to uncover new ways to enhance and expand both the clinical value of our knowledge and the return on prior investments in cancer research.





## A New Day for Anti-hormone Therapy

Hormones like estrogen, progesterone, testosterone and their derivatives influence the growth of certain subtypes of breast cancer and most cancers of the male and female reproductive organs (see **Fig. 17**). These hormones attach to specific proteins called receptors, in a lock-and-key fashion, which stimulate cancer growth and survival. This knowledge has provided insight into risk factors and treatments for some of these hormone-fueled cancers.

In breast cancer, for example, understanding that estrogen drives the approximately 70% of breast cancers that express the estrogen receptor led to the clinical development of anti-estrogen therapies. These drugs work in one of two ways. Some drugs, like tamoxifen, attach to the estrogen receptors inside cancer cells, blocking estrogen from attaching to the receptors. Other therapies, like aromatase inhibitors, lower the level of estrogen in the body so that the cancer cells cannot get the estrogen they need to grow. Anti-estrogen therapies have been extremely successful, as indicated by



## Antoni Smith

Age 57

Brooklyn, N.Y.

In 2007, I was diagnosed with prostate cancer. I was just 52 years old and a father of three. It progressed to metastatic cancer in 2010. By the end of March 2012, I had endured numerous rounds of chemotherapy, but my cancer was not responding. I was at the point of giving up. I agreed to try one last treatment, a brand new drug called abiraterone (Zytiga). It has given me a new lease on life—I'm feeling better than I have in a very long time.

Although I was told at diagnosis that my prostate cancer was aggressive, after receiving radiation and hormone therapy in 2008, I thought everything was going to be all right. But this was not the case. First, I lost my health insurance and was unable to continue with the anti-hormone therapy. Then, when I got my health insurance back a year later, I made the worst decision of my life: I refused to restart anti-hormone therapy because I felt great, and I did not want to suffer the side-effects of the treatment again.

Things gradually went downhill for me, and the metastasis to my kidney was discovered in 2010. By 2011, the cancer had spread to my bladder and lymph nodes, and I had my first kidney stent placed. One of my doctors suggested surgical castration, but I refused. Instead, I decided I needed another opinion, from a doctor at a facility dedicated to treating cancer patients. I chose Memorial Sloan-Kettering Cancer Center in New York City, and I entered their care in October 2011.

When I started the first of many cycles of chemotherapy, my PSA level was 700, which is 175 times higher than the level considered normal. The first chemotherapy combination had no real effect on my PSA level, and my cancer continued to spread. Increasing the dose of the chemotherapy drugs to the maximum and adding another drug to the cocktail did little, and my health declined dramatically. I suffered terribly with side effects from the chemotherapy drugs. I became dehydrated and lost a tremendous amount of weight as a result of diarrhea, vomiting and loss of appetite. I lost my hair. I experienced severe neuropathy in my feet and developed lymphedema. The side effects were so bad that I was hospitalized several times.

By March 2012, I did not have the strength to continue with the chemotherapy. I really believed that death was near. But my doctor at Memorial Sloan-Kettering Cancer Center said there was one more option I should try, abiraterone. I was reluctant. It has been the best thing that I have done. My hair, my strength and my appetite have all returned. I have not been hospitalized since being on abiraterone and my PSA level is down to 34. I still suffer from neuropathy in my feet and lymphedema, but thanks to my doctors and abiraterone I have my life back.

I hope that by telling my story, I can raise awareness of prostate cancer and of the fact that there is hope for other men facing the same situation as me.







## Memorial Sloan-Kettering Cancer Center

New York, N.Y.

- Is one of three NCI-designated comprehensive cancer centers in New York state.
- Employed 11,950 people in 2011.
- Admitted 24,486 inpatients and accommodated 535,900 outpatient visits in 2011.

Employee and patient data can be found in our 2011 annual report (to be published here in the next few weeks: <http://www.mskcc.org/annual-report>).

the fact that in women with early-stage estrogen receptor-positive breast cancer, tamoxifen treatment reduces the risk of disease recurrence by almost 50% and the chance of mortality by 30% (90).

The most exciting recent advances in understanding hormone-driven cancers have been made in the area of prostate cancer, the most commonly diagnosed cancer in the U.S. (3). It is estimated that there will be more than 240,000 new cases of the disease in 2012, and that more than 28,000 American men will succumb to it. Most prostate cancers, almost two out of every three, are diagnosed in men aged 65 or older, with African American men bearing a disproportionate burden of the disease (4). The knowledge that prostate cancer can be powered by hormones called androgens, like testosterone, provided the rationale for developing anti-hormone therapies called androgen-deprivation therapies. These therapies for prostate cancer work in similar ways to the anti-estrogen therapies used to treat breast cancer: They lower androgen levels or stop them from attaching to androgen receptors.

Androgen-deprivation therapies are most commonly used to treat advanced prostate cancer. Most individuals with this diagnosis respond very well to these treatments, and their cancers shrink or grow more slowly. Unfortunately, in most cases, the prostate cancers eventually stop responding to androgen-deprivation therapies and a more aggressive disease called castration-resistant prostate cancer arises, which has a very poor prognosis and urgently requires new treatment options.

While the most frequently used androgen-deprivation therapies reduce androgen levels, they do not eliminate these hormones completely. Basic research led to a better understanding of how the body manufactures and responds to androgens, which revealed a way to more completely block androgen production. This, in turn, led to the development of a groundbreaking new anti-androgen therapy, abiraterone (Zytiga), which the FDA approved in April 2011 for the treatment of metastatic castration-resistant prostate cancer. In a large-scale clinical trial, abiraterone significantly prolonged survival (91) and provided new hope to patients like **Antoni Smith**, p. 55. Ongoing clinical studies are examining whether abiraterone might provide a more effective treatment than the current standard of care for prostate cancer patients with less advanced disease. The results of one of these studies indicate that the presurgical use of abiraterone in patients with localized high-risk disease shows promise (92).

On August 31, 2012, the FDA approved a new androgen-deprivation therapy, enzalutamide (Xtandi, formerly called MDV3100). Enzalutamide attaches to androgen receptors and blocks their attachment to androgens. It is more effective than current drugs and has fewer side effects (93). The results of a recent large-scale clinical trial examining enzalutamide as a treatment for metastatic castration-resistant prostate cancer indicate that it significantly prolongs survival (94). These exciting findings are good news for patients who desperately need new treatment choices. Continuing research is assessing the potential of enzalutamide as a treatment for earlier stage prostate cancer.

Clinical research to further optimize the treatment schedule must be undertaken soon if patients are to gain the maximum benefit from recent progress in anti-hormone therapy. For example, the ideal sequence in which to administer these new drugs, when during the course of the disease to give them and the best combination of these and other treatments has yet to be determined. Moreover, despite the tremendous advances, some metastatic castration-resistant prostate cancer patients, like **S. Ward "Trip" Casscells, M.D.**, never respond to either abiraterone or to enzalutamide, and most individuals who do respond only do so temporarily. Additional new therapies are required for these patients, and further research efforts are essential if we are to meet this medical need.

"I believe it is incumbent upon each of us, especially those of us elected to serve, to do our part to rid this world of cancer."

### Representative Michael McCaul (R-TX)

Chair, House Childhood Cancer Caucus





## S. Ward “Trip” Casscells, M.D.

Age 60  
Washington, D.C.

“Gee, there are a lot of metastases here. What is your primary cancer?” These were the words that I heard back in 2001 from the radiologist looking at my MRI scans. I was shocked. I had never had a diagnosis of cancer and did not even suspect it. Since that day my prayers have been answered, and although none of the numerous treatments I have received—some through clinical trials—have cured my disease, they have gotten me to today. I am in my fifth remission.

A PSA test the day after I had received my MRI results revealed a PSA level of 94, which is more than 20 times higher than the level considered normal. A subsequent prostate biopsy showed that I had a highly aggressive prostate cancer that had already spread through my body. My doctors told me that the textbooks would say that I had just three years left, but they felt that if I was willing to endure a tough series of radiation, chemotherapy and anti-hormone therapies, they could get me eight years, maybe more. I was 49 years old, married with three young children, and of course I was going to fight it in any way I could.

I began treatment the day that I met my oncologist. He prescribed ketoconazole and promised me I would feel better the next day. I was very surprised because ketoconazole is usually used as an anti-fungal cream, but it turns out that it also rapidly reduces testosterone levels. I was amazed to find that sure enough it made me feel better overnight.

What followed was a treatment program of radiation and various chemotherapies. It was very hard on my body, but I responded very well. After six months, my PSA was undetectable, and I was in remission. I am very grateful that I had a doctor who believed that an aggressive course of treatment could benefit me and extend my life; I knew several people at the time who were not lucky enough to be offered these therapies, and they sadly passed away.

Over the next couple of years I had several recurrences, and each time I would have surgery to remove or chemotherapy to destroy the returning tumors. But after two years we ran out of treatment options, and I began participating in a series of clinical trials. Some drugs, like abiraterone (Zytiga), slowed or halted my disease for a time, while others, like MDV3100 (enzalutamide), seemed not to benefit me at all. Some people might consider my participation in these trials as unsuccessful because my disease kept progressing, but some of the therapies helped keep my disease in check for a few months. It is now more than 11 years since my diagnosis, and I am still working. I have seen my children grow up to become teenagers. I also believe that anything—any approved therapy, any drug under development and any dietary modification that has been suggested to be beneficial—that gives you a chance to live, even a little longer, buys time for a more successful treatment to be developed.

I hope that by sharing my cancer experience I can teach others the value of participating in clinical trials. I might have gained only a little benefit from the experimental drugs I received through the trials, but my involvement will ultimately help thousands of future patients. It is imperative that we—patients, doctors, researchers and those that make funding decisions—work together to make it easier to conduct clinical trials so that no stone is left unturned in the quest to improve the lives of cancer patients everywhere.

To find out more about Dr. Casscells’ experience with aggressive metastatic prostate cancer go to:  
[http://www.pcf.org/site/c.1eJRIRORepH/b.7937995/k.64B2/S\\_Ward\\_Trip\\_Casscells.htm](http://www.pcf.org/site/c.1eJRIRORepH/b.7937995/k.64B2/S_Ward_Trip_Casscells.htm)



## A New Day for Targeted Therapy

Our dramatically increasing knowledge of cancer biology at the molecular level is beginning to transform the standard of care from a one-size-fits-all approach to personalized cancer medicine, also called molecularly based medicine, precision medicine or tailored therapy. With this type of medicine, the molecular makeup of the patient and of the tumor dictate the best therapeutic strategy. The overall goal is to increase survival and quality of life for most cancer survivors.

The majority of the drugs recently approved by the FDA for cancer treatment are designed to precisely block the malfunctions that drive cancer growth. Many have been discussed above, as they specifically target molecules for which earlier drugs have provided tremendous patient benefit, but two—vismodegib (Erivedge) and ruxolitinib (Jakafi)—are unique because they oppose the function of cancer-driving molecules not previously targeted for therapy.

The development of vismodegib and ruxolitinib were the result of many research successes. These advances built upon a powerful knowledge base about cancer and represent a clear-cut example of the significant returns that are made on investments in such research.

Vismodegib is the first drug approved for the treatment of advanced basal cell carcinoma. Basal cell carcinoma is the most commonly diagnosed cancer in the U.S., estimated to affect about 2 million Americans annually (95). It is almost always curable with surgery; however, for the small fraction of patients in whom the cancer progresses to an advanced stage, there was no effective therapy until the FDA approved vismodegib in January 2012. Vismodegib is also the first drug that blocks a signaling network called the Hedgehog pathway, which fundamental research has determined is overactive in almost all basal cell carcinomas because of several different genetic mutations. With clinical trials showing that it dramatically shrinks tumors in most patients (96), like **Donna Johnson**, vismodegib is a welcome new treatment option for a condition for which there was a clear unmet need. Continuing clinical studies are assessing whether vismodegib might benefit patients with other types of cancers that have defects in the Hedgehog pathway, including pancreatic and lung cancers, amplifying the clinical value of the drug.



### Virginia G. Piper Cancer Center at Scottsdale Healthcare Scottsdale, Ariz.

Scottsdale Healthcare:

- Is the largest employer in Scottsdale, Ariz., with approximately 6,700 employees, 1,800 physicians and 1,300 volunteers.
- Has treated a total of 564,108 patients.
- Had an employee payroll of \$339 million in fiscal year 2011.
- Generated \$1.6 billion total economic output (direct and indirect) in fiscal year 2011.
- Is the co-lead site for Stand Up to Cancer pancreatic cancer research Dream Team.

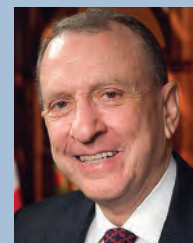
A similarly powerful example of drug development in the era of personalized cancer medicine began less than 10 years ago, when researchers discovered genetic mutations leading to excessive activity of a certain signaling network in most patients with myelofibrosis, a type of chronic leukemia for which there was no specific treatment. This discovery propelled researchers across disciplines to collaborate on the development of the first ever drug to precisely target this altered signaling network, called the JAK2 signaling network. The result of these endeavors was ruxolitinib (Jakafi), which the FDA approved for the treatment of myelofibrosis in November 2011, after several clinical studies showed that it significantly reduced symptoms, dramatically improving patient quality of life (97). Ongoing clinical studies are examining whether ruxolitinib might provide a viable treatment option for patients with other types of cancers with JAK2 signaling defects, including pancreatic cancer and certain subtypes of breast cancer.

The extraordinary progress that has been made in recent years toward developing drugs that precisely target the molecular defects driving cancers has already made a real difference in the lives of a growing number of cancer patients, the more than 13 million cancer survivors in the U.S., and their families and loved ones. Despite these advances, diseases like pancreatic and liver cancers still represent major killers, and they have no effective molecularly targeted therapies. In the case of pancreatic cancer, fewer than one

“I believe medical research should be pursued with all possible haste to cure the diseases and maladies affecting Americans. I have said many times that the NIH is the crown jewel of the federal government – perhaps the only jewel of the federal government.”

### Senator Arlen Specter (R-PA)

Former Chair and Ranking member of the Senate Appropriations Subcommittee on Labor- HHS-Ed, and a cancer survivor







## Donna Johnson

Age 61

Colorado Springs, Colo.

I am a two-plus year survivor of metastatic basal cell carcinoma. The drug vismodegib (Erivedge) saved my life and renewed my hope that I can continue on this path to a full and vibrant existence.

I was diagnosed with basal cell carcinoma in 2006 and did not think too much about it after the tumor had been surgically removed. My doctors assured me that it was a type of cancer that almost never spreads to other parts of the body, and we all thought that everything would be okay.

How wrong we were. In 2010, after experiencing tremendous pain in my shoulder and neck, my doctor discovered that my basal cell carcinoma had recurred internally. It was not visible on my skin but had invaded my shoulder and neck tissues. I had surgery, during which surgeons scooped out most of my shoulder and neck and removed a lot of my collarbone. They used muscle from my breast to hold my shoulder in place.

The surgery gave me some relief, but the pain returned in early 2011. An MRI scan in April revealed that the cancer had come back with a vengeance. I saw several doctors in Colorado who told me there was little they could do. One suggested cutting the nerves to my shoulder to relieve the pain, while another told me amputation was the only option. I was in unbearable pain—high doses of oxycodone did nothing for me. I was desperate.

My life changed after my stepfather in Arizona told me about a clinical trial for metastatic basal cell carcinoma that he had read about in a local paper. I immediately contacted the center that was running the trial and got enrolled. I began receiving treatment, the test drug vismodegib, at the Virginia G. Piper Cancer Center at Scottsdale Healthcare, in Arizona, at the end of August 2011. By the end of September I had stopped taking all my pain medications. It was unbelievable how quickly my life had turned around.

Not only did vismodegib rapidly eliminate my pain, it also made me feel better all around. One of my affected lymph nodes was three inches in diameter when I started the clinical trial; it had shrunk by 50% within a month. Today, having been taking the drug for almost a year, I can say that my cancer has stopped progressing and that all my tumors are receding. I attribute this almost exclusively to vismodegib, although I did have a six week course of radiation to help things along in March 2012. I live with side effects of the drug—hair loss and muscle cramp—but these are minor compared with pain that I experienced before.

I continue to take vismodegib once a day and will have to do so for as long as it keeps my cancer at bay. But that has become much easier since the FDA approved the drug in January 2012 and I no longer have to travel to Arizona to receive it. My doctors have told me that it is likely that my cancer will be smarter than the drug that I take and that it will eventually return. But I remain hopeful. There are so many amazing minds out there working on the problem that I believe it is only a matter of time before yet more doors are opened to new treatment options.

So what wisdom can I share from my cancer experience? Be your own advocate. Educate yourself about clinical trials because your doctor doesn't know everything and new treatment options are always being developed. And most importantly keep fighting. I am living proof that it is possible to regain your life.



## Jill Ward

Age 54  
Henrico, Va.

I will become a five-year survivor of pancreatic adenocarcinoma in October. While I am excited to reach this milestone, I realize that I will be one of very few who do. Pancreatic cancer is the only major cancer with a five-year survival rate in the single digits. This is why I advocate for pancreatic cancer research through the Pancreatic Cancer Action Network.

I was diagnosed with pancreatic cancer in October 2007, just a few days shy of my 50th birthday. My father had died from the same disease in 2004. I had begun losing weight and experiencing diarrhea. An urgent care physician and my regular doctor both told me that it was unlikely that I had pancreatic cancer because I was young, I did not smoke, I rarely drank alcohol and the disease was not hereditary. My doctor ordered a blood test to assess my liver function, and when the results came back abnormally high, I was referred to a gastroenterologist. After several liver conditions were ruled out, a special procedure revealed that there may be a tumor in my pancreas.

Because it is very hard to see the pancreas in scans, the next step was a complicated surgery called the Whipple procedure. The results from the biopsy showed that I had stage II pancreatic cancer. I knew from my research that my chances of long-term survival were not good, so my husband and I decided that we were going to prioritize making memories and having fun with our children.

After the surgery, I had six weeks of radiation combined with a continuous infusion of chemotherapy. I found it difficult to find a knowledgeable oncologist because pancreatic cancer is a relatively rare cancer and few patients survive to be treated long term. When I discovered that my first oncologist did not know the standard treatment for pancreatic cancer, I changed doctors. In 2008, my second oncologist insisted that new and growing nodules in my lungs were not metastatic tumors and would not authorize a biopsy.

At this point, I went to the Johns Hopkins Hospital, in Baltimore. There I met one of the top researchers in the pancreatic cancer field. He immediately arranged for me to have a lung biopsy. The results were discouraging: The cancer had metastasized to my lungs. I knew that my odds of surviving had shortened dramatically. So, in keeping with our vow to enjoy life, my husband and I gathered our three children, packed up our van and drove to Key West for a vacation.

Over the past four years, I have been on several different chemotherapy regimens, each decided upon by both me and my oncologist. I am now on my sixth regimen. As this may be the last option available to me, I am utilizing the Pancreatic Cancer Action Network and my oncologists to search for a clinical trial in which to participate.

Throughout my experience with cancer, my philosophy has been to enjoy life and to trust that everything will work out as it should. One oncologist has repeatedly suggested that I stop chemotherapy. I tell him that yes, chemotherapy does have rough side effects, but that I'm still having fun and am determined to be aggressive in pursuing treatments until that is no longer true.

When I was diagnosed in 2007, I was determined to see all of my children graduate from high school. Now, thanks to my current top-notch medical team and treatments, I am making plans to see my youngest children graduate from college.





### The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins Baltimore, Md.

- Is the only NCI-designated comprehensive cancer center in Maryland.
- Employs approximately 1,200 faculty and staff.
- Johns Hopkins experts provide services to approximately 7,000 newly diagnosed cancer patients each year.
- Johns Hopkins and affiliated institutions in Maryland have a total economic impact of nearly \$10 billion in fiscal year 2010.

in 16 patients are living five years after diagnosis (3). **Jill Ward**, who is about to celebrate her fifth year of survivorship, is a rarity. Much more work needs to be done if the outlook for those diagnosed with this disease is to improve. For some time, researchers have known the identity of a predominant cancer-driving molecular defect, but they have been unable to successfully develop drugs that precisely target it. They are actively looking for ways around this obstacle. One approach that basic research suggests might have promise is combining two molecularly targeted drugs that are specific for different signaling network components (98), and this idea is currently in the early stages of being tested in clinical studies.

Combinations of molecularly targeted drugs are also being investigated as potential new approaches to treating cancers other than pancreatic cancer. For example, a drug that blocks the mutated B-RAF protein, which is the molecular defect found to drive more than 50% of melanoma cases, has revolutionized the treatment of this deadly disease (99); however, these cancers eventually acquire resistance to the drug and they progress (see **Fig. 16**, p. 50 and **Sidebar on Drug Resistance**, p. 49). Melanoma research has identified several molecular pathways that bypass the inhibition of mutated B-RAF, and recently initiated clinical studies are assessing whether adding a second drug that precisely targets one of these resistance signaling networks will further prolong survival in patients who have experienced progression. The results are eagerly awaited.



In 2011, the Nobel Prize in Physiology or Medicine was awarded for research discoveries that furthered the understanding of the immune system and influenced immunotherapy for treating cancer.

## A New Day for Immunotherapy

Over the past four-plus decades, cancer researchers have accumulated a tremendous understanding of the complexity of cancer. It is now evident that while the genetic alterations in cancer cells have a profound effect on the development of cancer, cancer cells can also modify their surroundings, often called the tumor microenvironment, enhancing the growth and spread of the cancer.

A key component of the tumor microenvironment is the immune system. Research has determined that in some cases, the immune system completely eliminates a cancer before it becomes clinically apparent. This fact is central to the idea that it might be possible to develop therapies that train a patient's immune system to destroy a cancer. Putting this into clinical practice, however, has proven extremely challenging. Recent scientific advances have revealed one of the reasons for this phenomenon, i.e., that tumors have developed many sophisticated ways to block their own destruction by the immune system. Progress in our understanding of the approaches that tumors use to escape elimination is finally converging with advances in our basic understanding of the immune system to yield multiple new strategies that have the potential to revolutionize cancer treatment.

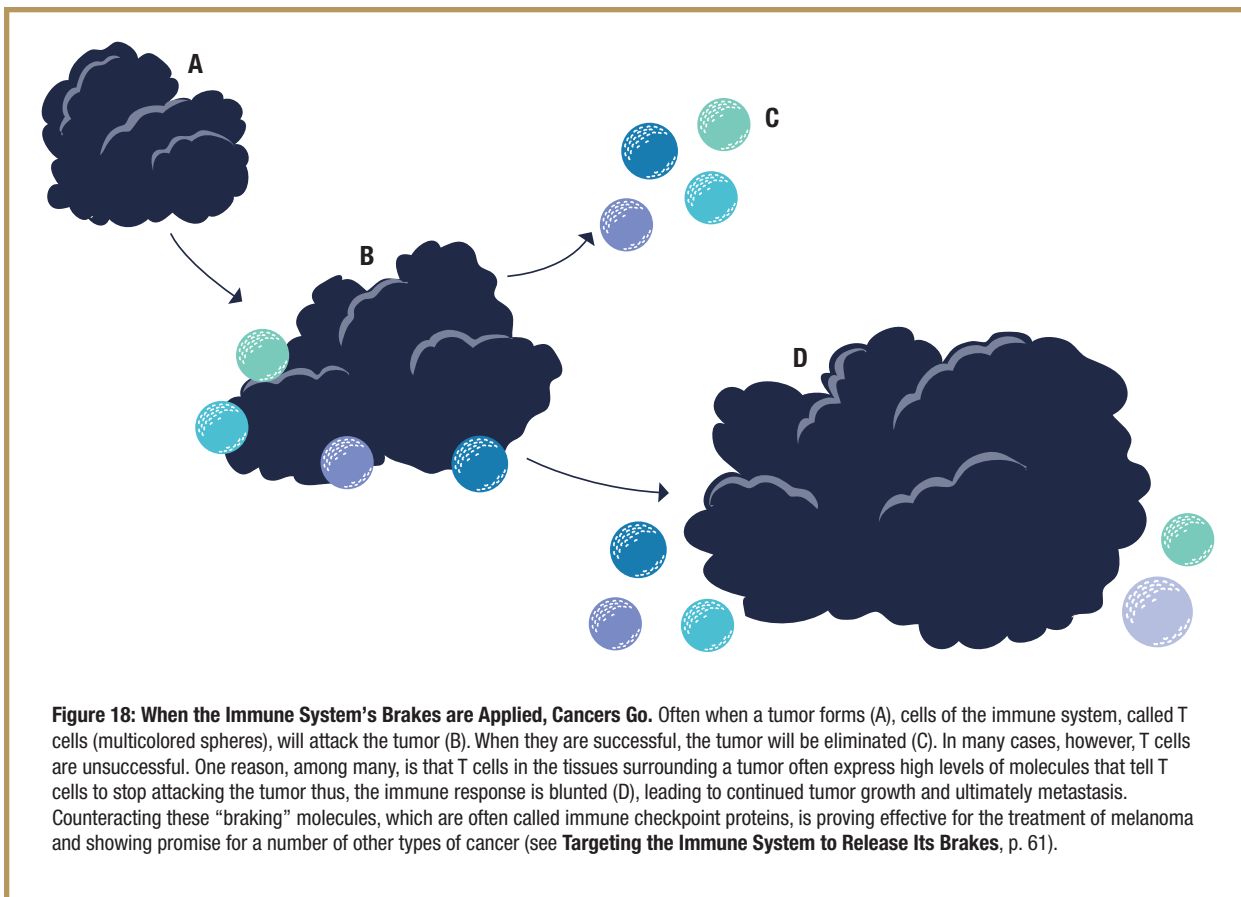
Cancer treatment that alters the immune system is called immunotherapy. Not all immunotherapies operate in the same way, however, and the ongoing discovery of the many intricacies of the immune system is continuing to open new pathways to the development of novel treatment strategies. Among the immunotherapy approaches currently saving patient lives are some that seek to boost the natural cancer-fighting ability of the immune system by taking its brakes off, some that enhance the killing power of the patient's own immune cells and others that flag cancer cells for destruction by the immune system. The first approach—using therapies that boost the immune system by taking its brakes off—is now leading the field of immunotherapy, producing remarkable and durable responses in cancers that are not amenable to standard treatments. However, other approaches are starting to gain traction as well after many challenging years of development.

### Targeting the Immune System to Release Its Brakes

It is well established that immune cells called T cells are naturally capable of destroying cancer cells and that this ability can be suppressed by the tumor. One explanation for this was provided by the discovery that T cells in the tissues surrounding a tumor express high levels of molecules that tell T cells to slow down and to stop acting aggressively (see **Fig. 18**, p. 62). This finding led researchers to seek ways to counteract these molecules, which are often called immune checkpoint proteins.

The most well-understood immune checkpoint protein is called CTLA-4, and a therapeutic antibody, ipilimumab (Yervoy), which targets CTLA-4, was approved by the FDA in March 2011 for the





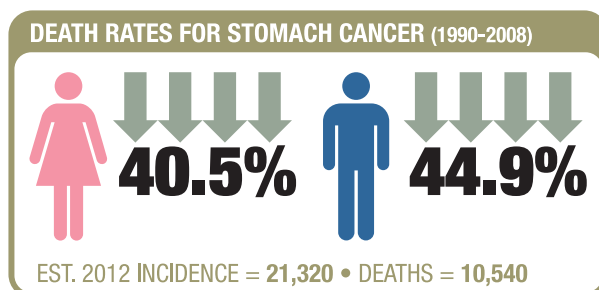
treatment of metastatic melanoma. Ipilimumab releases the brakes on T cells and significantly prolongs survival (100). Some patients, like Andrew Messinger (who was featured in the AACR Cancer Progress Report 2011), are still gaining benefit from it more than three years after starting therapy (101). Ongoing clinical studies are examining whether ipilimumab might be effective against other cancers. Early results in patients with advanced lung cancer are encouraging, but need verification in larger numbers of patients (102).

The development of ipilimumab highlights the power of continued investment in research: CTLA-4 was first identified in 1987, but it took almost 25 years of scientific endeavor before it became an FDA-approved therapeutic target. In addition, the tremendous success of this novel therapeutic antibody has inspired the ongoing development of therapies directed toward other immune checkpoint proteins, including one called programmed death-1, or PD1 (see **Sidebar on Immune Checkpoint Therapeutics**, p. 63). The effects of a therapeutic antibody that targets PD1, as well as one that targets the protein to which PD1 attaches, called PDL1, are currently being assessed in clinical trials. The early results are very promising (103, 104) and indicate that ipilimumab has blazed the way for a family of similar effective therapies.

### Targeting the Immune System to Boost Its Killing Power

Another recent development in immunotherapy for cancer treatment is using strategies to enhance the ability of a patient’s own immune cells to eliminate cancer cells. This can be done in several ways, including giving a patient a vaccine to program their own immune system to recognize and destroy their cancer or by growing the patient’s immune cells in the laboratory and reprogramming them to recognize and destroy their cancer. The latter are treatments collectively called adoptive immunotherapies.

Sipuluecel-T (Provenge) is the only FDA-approved therapeutic cancer vaccine. It is used to treat metastatic castration-resistant prostate cancer, after it was shown to prolong patient survival



## Immune Checkpoint Therapeutics

Ipilimumab, which targets an immune checkpoint protein called CTLA-4, significantly prolongs survival in patients with metastatic melanoma. This success led to the development of therapies that target another immune checkpoint protein, called programmed death-1, or PD1, as well as those that target the protein to which PD1 attaches, PDL1. These have been tested in early stage trials with some success.

A recent small-scale trial of 296 patients showed that an antibody to PD1 on the surface of immune cells, called T cells, was able to produce complete or partial elimination of tumors in 18% of non-small cell lung cancer patients, 28% of melanoma patients, and 27% of renal cell cancer patients. Perhaps most importantly, the reduction in tumors lasted for at least a year in nearly 65% of responding patients (103).

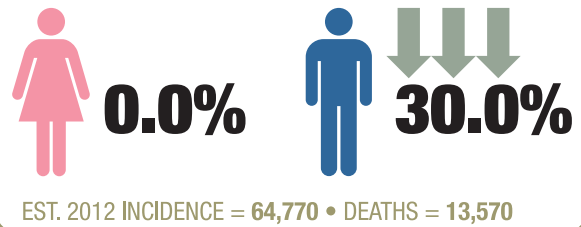
Similarly, a phase I trial of 207 patients treated with an antibody to PDL1 produced complete or partial elimination of tumors in 17% of patients with melanoma, 11% of renal cell cancer patients, and 10% of non-small cell lung cancer. Further, in patients followed for more than one year, at least 50% had reductions in tumors lasting at least one year (104).

(105). It is a cell-based immunotherapy, wherein each treatment is customized for the patient and helps direct their immune system to destroy their cancer cells. While only an early success, it provides hope that other effective cancer treatment vaccines can be developed. As such, this is an intensively studied area of cancer research. In the U.S. alone, more than 300 clinical trials testing cancer vaccines are actively recruiting patients.

Adoptive immunotherapies are complex medical procedures that are built upon our accumulating knowledge of the biology of the immune system, in particular, T cells. The first step is to harvest a defined population of T cells from the patient. T cells that target the patient's cancer are then selected from the harvested population or generated by genetic engineering, grown in very large numbers and then returned to the patient's body, where they fight the cancer.

There are no FDA-approved adoptive immunotherapies, but at the NCI, one procedure using T cells harvested from a patient's own surgically removed tumors has been used to treat metastatic melanoma for more than 20 years (106). During this period, the treatment protocol has been refined many times, as scientific and technological advances have facilitated improvements, and about 20% of patients, including Roselyn Meyer (who was featured in the AACR Cancer Progress Report 2011), now achieve long-term remission (107). Despite these successes, the NCI adoptive

### DEATH RATES FOR LARYNX (1990-2008)



immunotherapy treatment is not yet considered standard of care; it remains an area of active research and is only available to patients enrolled in clinical trials.

The effectiveness of numerous other adoptive immunotherapies is currently being assessed in various clinical trials for several types of cancer. Very early clinical studies of an adoptive immunotherapy for the treatment of chronic lymphocytic leukemia recently showed that the strategy has tremendous promise (see **Sidebar on Adoptive Immunotherapy for Chronic Lymphocytic Leukemia**) (108), but more patients need to be treated to confirm this. Additional new adoptive immunotherapies with enhanced ability to yield patient benefit are likely to emerge in the near future as our understanding of T cells and how they combat cancer increases.

### Directing the Immune System to Cancer Cells

Therapeutic antibodies have been saving the lives of cancer patients since 1997, when the FDA approved rituximab (Rituxan) for the treatment of certain forms of non-Hodgkin's lymphoma. More than a dozen therapeutic antibodies have been approved by the FDA for use against several cancers (see **Table 6**, Appendix) and many more are in clinical trials.

## Adoptive Immunotherapy for Chronic Lymphocytic Leukemia

A recent report indicates that adoptive immunotherapy holds promise as a treatment for chronic lymphocytic leukemia (134). In this study, immune cells, called T cells, were harvested from three patients and genetically modified in the laboratory so that they would not only attach to a protein expressed by the leukemia cells, called CD19, but also be triggered to attack the cancer cells when they did so. The number of modified T cells was expanded in the laboratory before they were returned to the patients. These cells were still detectable and functioning as expected in the patients six months later. Moreover, the patients were still in remission at the time the report was published, which was 10 months after their treatment.

## Brooke Mulford

Age 7

Salisbury, Md.

A message from **Amy Mulford**, Brooke's mother.

My daughter Brooke was diagnosed with a very aggressive cancer, stage IV high-risk neuroblastoma, on January 5, 2009, when she was just four years old. Since that awful day she has endured all kinds of grueling cancer therapies, but we are fortunate that she was able to receive a combination immunotherapy treatment that included a drug called Ch14.18. It gave her a chance that children before her did not get.

It all started on Christmas Eve 2008, when Brooke started limping and complaining of pain in her leg. Her pediatrician diagnosed a sinus infection and infections in both her ears, and sent us to the local hospital for blood work and X-rays. Hospital doctors said that she had toxic synovitis as a result of the sinus and ear infections and that all she needed was antibiotics. A week later, I knew that was not the case when, after a three-hour car journey to visit family in New Jersey, she was unable to straighten her legs, in unbearable pain and running a fever. We went to Children's Hospital of Philadelphia (CHOP), and it was there that she was diagnosed.

We were very lucky to have been at CHOP. Neuroblastoma is rare; fewer than 700 American children are diagnosed with the disease each year, but a significant number of these children are treated at CHOP. Doctors determined that Brooke's cancer had started in her right adrenal gland and had spread through pretty much every bone in her body and approximately 80% of her bone marrow. I had seen the cancer light up throughout her body on her MIBG scan, and I thought there was no hope that she could survive. But, as a result of their experience with the disease, the doctors at CHOP were able to reassure us that there were treatments and that survival was a possibility.

Brooke's treatment began a week after her diagnosis. After six rounds of chemotherapy and surgery to remove the tumor on her adrenal gland, her MIBG scan showed that she had responded very well to the chemotherapy, but the cancer was not completely gone. However, after two stem cell transplants, using stem cells that they harvested after the second round of chemotherapy, her MIBG scan showed no evidence of neuroblastoma.

Right before the second transplant we found out that interim results of an ongoing clinical trial had shown that a combination immunotherapy that included the therapeutic antibody Ch14.18 increased cancer-free survival dramatically, and that Brooke was eligible to join the trial and receive this groundbreaking treatment. So, in November 2009, after the 12 rounds of radiation therapy that had followed her second transplant, she started on Ch14.18. She was lucky. While the treatments were painful and she had issues with her blood pressure, among other things, she did not experience the excruciating pain that other children do and she was able to complete the full six-month course of the combination immunotherapy.

Brooke completed all her treatments in April 2010, and there is currently no evidence of her disease. She now has scans every six months, and we hope that they continue to be clear.

I am so thankful that Brooke had this chance of survival, and I have no regrets about putting her through such a punishing course of treatments. However, it was devastating to watch her go through it and she has to endure a lot of side effects from the treatments—she has problems with her vision and her thyroid, issues with her teeth, permanent hair loss, trouble with coordination, and she will be infertile. Much more research needs to be done so that other children do not have to endure what Brooke did to be given a chance at life.







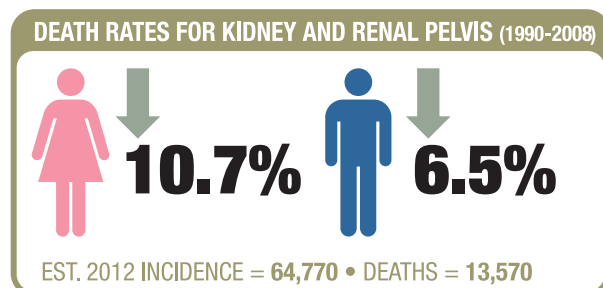
### The Children's Hospital of Philadelphia Philadelphia, Pa.

- Admitted 28,000 inpatients and had more than 1.1 million outpatient visits in fiscal year 2011.
- The Cancer Center comprises 43 full-time pediatric oncologists, 54 physicians and scientists in complementary disciplines, 22 oncology nurse practitioners, 150 Oncology nurses, 6 social workers and 11 child life specialists.

A therapeutic antibody is a protein that attaches to a defined molecule on the surface of a cell. These agents can exert anticancer effects in several different ways. For example, they can block cancer-driving signaling networks initiated by the specific molecule to which they attach, and they can work by attaching to cancer cells expressing their target, flagging them for destruction by the immune system. Therapeutic antibodies that flag cells for the immune system are a form of molecularly targeted immunotherapy, and they include an experimental medicine, called Ch14.18, that is showing promise as a treatment for high-risk neuroblastoma.

Immunotherapy with Ch14.18, in combination with two factors that also boost the killing power of the immune system, has been shown in clinical trials to increase dramatically—by 20 percentage points—the chance that a child with high-risk neuroblastoma will be cancer free two years later (109). Although this treatment strategy is not FDA approved, it is at the forefront of care for a group of patients who have a tremendous need for new treatment options; fewer than one in every two children diagnosed with high-risk neuroblastoma live five years (110).

Despite the tremendous success of the Ch14.18 combination immunotherapy, which is enabling some children, like **Brooke Mulford**, to live disease free, the treatment is associated with significant toxicities. They can be so severe that some children cannot complete the treatment course, while those who do, suffer lasting negative side effects. Ongoing basic and clinical research is seeking ways to mitigate these severe side effects as well as to identify those children most likely to benefit from treatment or those least likely to respond, so that the latter can be spared from futile and potentially noxious therapies.



## A New Day for Patient Stratification

The rapid pace of scientific and technological innovation over the past few decades has made it possible to link specific genetic mutations to distinct behaviors of individual cancers. As a result, we now have the ability to understand that two patients with what is described clinically as a single disease, say lung cancer, may actually have two completely different cancers at the molecular level. Thus, these patients may have two very distinct courses of disease over time, and will therefore require entirely different molecularly targeted drugs (see **Fig. 19**, p. 67).

Our arsenal of precisely targeted cancer drugs is expanding each year. However, the effective therapeutic use of these drugs often requires a test, called a companion diagnostic, that can accurately match patients with the most appropriate therapies. Patients positively identified by the 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 treatment costs associated with their adverse effects.

Many molecularly targeted cancer drugs have been FDA approved without a companion diagnostic. In August 2011, however, the FDA approved a drug/test pair that is now benefiting a defined group of lung cancer patients. The drug, crizotinib (Xalkori), blocks the signaling molecule ALK. It was developed after fundamental research established that genetic aberrations that lead to altered ALK expression and activity drive some lung cancers. Crizotinib dramatically improves the survival of patients with *ALK* gene defects, like **Monica Barlow**, p. 66 (111). However, these individuals make up fewer than 7% of all patients diagnosed with the most common form of lung cancer, non-small-cell lung cancer. Without the companion diagnostic, this small population of patients would not be identified, making crizotinib clinically useless because the patient and financial costs would far outweigh the benefits.

The success of crizotinib and the importance of its companion diagnostic emphasize the value of having a way to identify those patients with a high likelihood of responding to a particular drug, and many molecularly targeted drugs for cancer treatment are now being developed side-by-side with a companion diagnostic.

Additional clinical tests to divide patients with a given cancer into therapy groups based on the molecular characteristics of their individual cancers are urgently needed because not all patients with a given genetic defect will benefit from a drug targeting that alteration. For example, while genetic alterations that result in cancers driven by a specific cell surface protein called EGFR are found in 10% of non-small-cell lung cancers (112) and in almost



## Monica Barlow

Age 35

Ellicott City, Md.

I was diagnosed with stage IV lung cancer in September 2009. I was blown away by the diagnosis: I was just 32, I had never been a smoker, I had no family history of cancer, and I had always maintained a healthy lifestyle. I feel very fortunate, however, that my doctors were able to find a specific mutation in my cancer that meant I would likely benefit from the drug crizotinib (Xalkori). I've been taking crizotinib since Thanksgiving 2010, and my cancer is under control. I feel great and have a good quality of life.

I first experienced symptoms during the summer of 2009. I had a cough that I could not shake, despite several courses of antibiotics. I was short of breath when running, which I was doing a lot of because I was training for a half marathon. Eventually, my husband persuaded me to get it checked out. I went to a walk-in clinic at the University of Maryland Medical Center. The doctor I saw there told me I should get a CT scan. I had that done soon after. It showed a nodule in the left lobe of my lung.

A bronchoscopy followed, which showed the nodule was cancer, and then a PET scan, which showed the cancer had spread to some of my lymph nodes and my liver. Surgery was not an option, so my doctors started me on the drug erlotinib (Tarceva), which works against a protein called EGFR. They did this because many lung cancers in patients who are young, otherwise healthy and have never smoked have EGFR mutations. It turned out that I did not have EGFR mutations, and erlotinib did not work for me.

At about this time, I got a second opinion and transferred my care to Johns Hopkins. I received great care at the University of Maryland, but I knew that with my condition I would probably need access to clinical trials and more of them were available at Johns Hopkins.

Since the erlotinib was not working, I was switched to a chemotherapy regimen. I received six cycles of carboplatin, pemetrexed (Alimta) and bevacizumab (Avastin). My cancer responded well; the nodule in my lung shrank and those in my liver were kept under control, so I came off this treatment and just took Avastin.

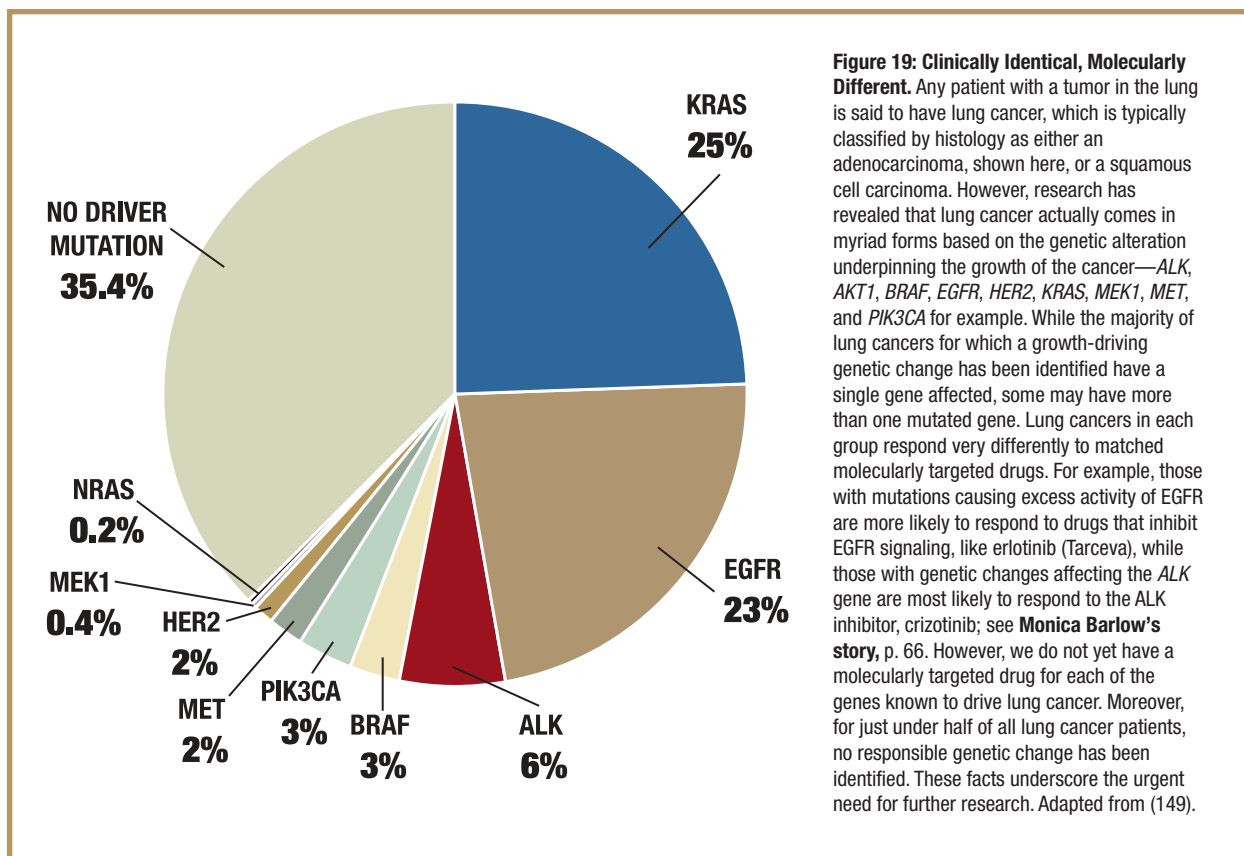
In the meantime, my doctors discovered that my cancer had the ALK mutation, and they were debating whether or not I should enroll in a clinical trial testing crizotinib, which targets ALK. Since I was still responding well to the Avastin, I stayed on that until October 2010, when the tumors in my liver started growing. It was at this point that I switched to the crizotinib clinical trial, and I've been taking the drug ever since.

Although crizotinib has worked really well on the tumor in my lung and on my affected lymph nodes, the tumors in my liver have been problematic. I had several procedures on my liver to try and get rid of the tumors before having surgery, in May 2012, to remove the 40% of my liver that has been affected over the course of my disease. My only scan so far since the surgery has shown that my liver is cancer free, and right now my life is almost the same as it was before my diagnosis.

I know that I probably would not be alive right now without crizotinib, and I am a huge advocate of research. I just hope that it advances faster than my cancer.







**Figure 19: Clinically Identical, Molecularly Different.** Any patient with a tumor in the lung is said to have lung cancer, which is typically classified by histology as either an adenocarcinoma, shown here, or a squamous cell carcinoma. However, research has revealed that lung cancer actually comes in myriad forms based on the genetic alteration underpinning the growth of the cancer—*ALK*, *AKT1*, *BRAF*, *EGFR*, *HER2*, *KRAS*, *MEK1*, *MET*, and *PIK3CA* for example. While the majority of lung cancers for which a growth-driving genetic change has been identified have a single gene affected, some may have more than one mutated gene. Lung cancers in each group respond very differently to matched molecularly targeted drugs. For example, those with mutations causing excess activity of EGFR are more likely to respond to drugs that inhibit EGFR signaling, like erlotinib (Tarceva), while those with genetic changes affecting the *ALK* gene are most likely to respond to the ALK inhibitor, crizotinib; see **Monica Barlow’s story**, p. 66. However, we do not yet have a molecularly targeted drug for each of the genes known to drive lung cancer. Moreover, for just under half of all lung cancer patients, no responsible genetic change has been identified. These facts underscore the urgent need for further research. Adapted from (149).

50% of glioblastomas (113) (the most common and most aggressive brain tumors in adults), drugs that precisely target EGFR provide benefit only to the non-small-cell lung patients (112, 113). Many researchers are seeking to understand why this is and to establish ways to better predict whether or not a patient with an EGFR genetic alteration will respond to EGFR-targeted drugs. Early findings suggest that more specifically characterizing the type of genetic mutation that is responsible for the cancer might provide one way to more precisely forecast the drug response (112, 113).

Variability in initial responsiveness to a particular molecularly targeted therapy occurs between two types of cancer with apparently identical molecular underpinnings and also between two patients with the same cancer type and the same cancer-driving molecule. Therefore, it is now clear that tests that look for the presence or absence of a single molecular defect are insufficient to definitively predict a patient’s response to a drug. In some instances, this occurs because of other malfunctions in the molecular machinery of the cancer cells themselves. For example,



People who smoke 1–2 packs of cigarettes a day are about **22** times more likely to die of lung cancer than non-smokers.

clinical studies found that certain drugs that target EGFR can prolong the survival of patients with metastatic colorectal cancer, but only if the cancer cells express the normal form of the protein KRAS (114). Unfortunately, about four out of every 10 colorectal cancers have a mutated form of KRAS. So, since July 2009, the FDA has required the use of a KRAS test, one of which was just approved by the FDA in July 2012, prior to giving a patient an EGFR-targeted drug for the treatment of metastatic colorectal cancer. Thus, the use of two tests to characterize the molecular subtype of a patient’s individual cancer can help avoid unnecessary exposure to the side effects of potentially ineffective treatments.

For most cancers it is unlikely that two tests alone will be sufficient to predict a patient’s response to a molecularly targeted drug because it is highly unlikely that a second indicator of response will be present in as large a fraction of the patient population as mutated KRAS is in metastatic colorectal cancer patients. Identifying panels of response predictors, or biomarker signatures (see **Sidebar on Pharmacogenomics**, p. 68), through the use of advanced genome sequencing technologies, is an area of intense research investigation, as these panels hold the promise of dramatically increasing the precision of cancer medicine.

While not based on wholesale genomic analysis, there are currently two multi-gene test panels used by clinicians to help them tailor their approach to treating women with certain forms of early-stage



## Lori Redmer

Age 44

Westport, Conn.

Nothing prepared me for the shock of being diagnosed with stage III breast cancer, let alone the fact that it was triple-negative breast cancer, a form of the disease that we fight today with almost the same tools that we used in the 1970s.

My journey with cancer began right before the holidays in 2009. One morning I woke up with pain in one of my breasts. At first I wasn't concerned, because "cancer doesn't hurt," but I went to see my doctor to be sure. After tests, I was told that I had what looked like a large cancer in my left breast, and that I needed to see a surgeon immediately. It was like running into a wall at a thousand miles an hour.

The news got worse, much worse, before it started to get better. Six days later I had a lumpectomy. Waking up and getting the news that it was definitely cancer was another blow. Then the results of the pathology showed that my cancer was triple negative. The oncologist who gave me the news said, "I had hoped for better for you. You got the bad player." Those are words you never want to hear from an oncologist. Another surgery revealed I also had five affected lymph nodes.

I looked fine. I felt fine. It was just so surreal that this lurking threat could really compromise everything for me. I had to wait two weeks for the results of the scans and tests that would tell me if I had metastases. They were the darkest days of my life. I knew that if the results were bad, my deterioration would likely be rapid and my 14-month-old youngest child probably would not even remember me.

The tide turned when I learned that I had no metastases. At that point I just got down to business. I knew that I could deal with the physical side of things but that I would have to equip myself to face the mental side—the fear of recurrence and the uncertainty about the future. I leaned heavily on my faith, but I also learned to meditate and started running. I ran my first marathon a little less than a year after my diagnosis.

I was just 42 when I was diagnosed, which is fairly young, but typical for triple-negative breast cancer. I got a lot of guidance from the Triple Negative Breast Cancer Foundation just after diagnosis. I was also lucky to connect with a group of eight other young women with breast cancer for support. But I am unique within the group. Most were ER/PR-positive, a couple were HER2-positive and some were triple-positive. I was the only triple-negative. My terror was different—a higher risk of recurrence and fewer tools in the fight.

Sometimes people think breast cancer is not as bad as it used to be. That might be true for the majority of breast cancers, for which there are targeted therapies. But breast cancer is not one disease, it is many diseases, and triple-negative breast cancer affects a huge swath of women in the prime of their lives. For us, there are no targeted therapies available. Hopefully, the name "triple-negative breast cancer" will become obsolete in a few years because we will discover the next receptor. And then we will find a way to take this breast cancer down. Right now I am working toward that goal as the Executive Director of the Triple Negative Breast Cancer Foundation. Turns out I wanted to beat it AND join it!





## Pharmacogenomics

Each person's body handles drugs differently. These differences are a result of subtle variations in the genome of each individual. The use of advanced genome sequencing technologies to study the influence of genetic variation on patients' responses to drugs is an area of research called pharmacogenomics. The goal is to develop genetic signatures that can be used to predict drug response and thereby optimize drug therapy in order to ensure maximum efficacy with minimal adverse effects.

breast cancer. The tests, a 21-gene test called *Oncotype DX* and a 70-gene test called *MammaPrint*, estimate the likelihood of cancer recurrence at a distant site. Clinicians can use this information as they decide whether anti-hormone treatment alone is likely to be sufficient or whether a chemotherapeutic drug should also be used. Although clinicians already use both tests, they are undergoing further testing in clinical trials to help refine and expand their utility. It is envisaged that near-term progress in genomic medicine should yield additional clinically applicable gene signatures to guide therapeutic decision-making and tailoring of a patient's treatment plan.

## A New Day for Genomic Medicine

The explosion of genetic information and our ever-increasing understanding of how to apply it are providing patients with some forms of cancer less toxic and more effective treatment options, thereby realizing the promise of personalized medicine.

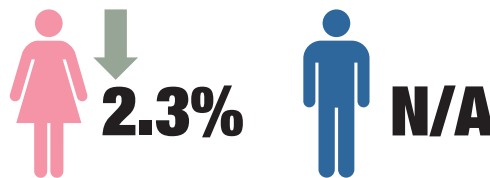
Many major advances are highlighted in this report, but gaps in our knowledge remain. For example, there are many forms of cancer, including liver and pancreatic cancers, for which we have insufficient genetic and/or technical knowledge to design effective molecularly targeted therapies. Even for those cancers for which there is a therapy that precisely targets an underlying cancer-driving molecular defect, not all patients' cancers harbor the matching molecular malfunction, so not all patients will benefit



### Norwalk Hospital Norwalk, Conn.

- Employs 1,800 people.
- 14,872 patient discharges and 240,361 outpatient visits.
- Diagnoses approximately 700 new cancers per year, 200 of them being breast cancer.
- Provided net community benefits of \$27,481,152 between October 1, 2010 and September 30, 2011.

### DEATH RATES FOR CORPUS AND UTERUS, NOS (1990-2008)



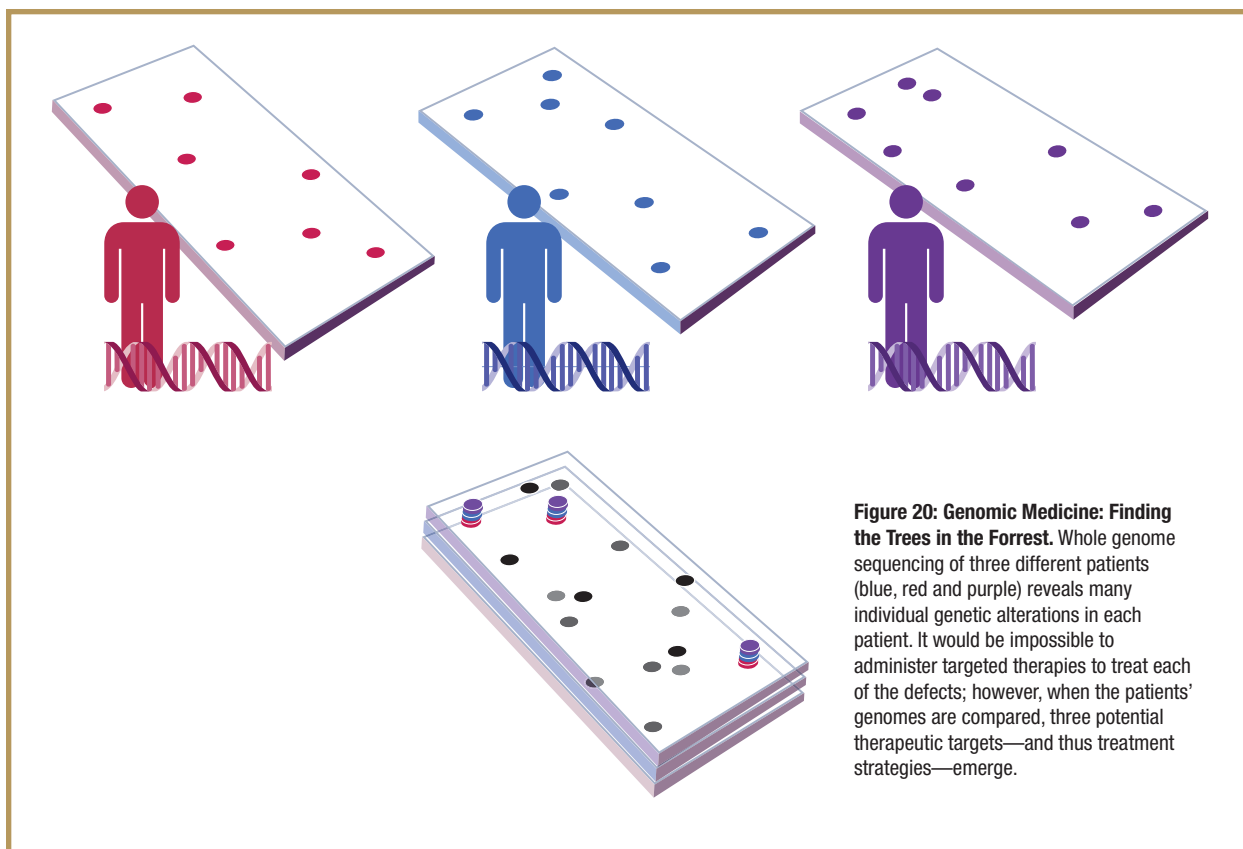
EST. 2012 INCIDENCE = 47,130 • DEATHS = 8,010

from the drug. Breast cancer is a clear case in point. Women whose breast cancers have a genetic alteration that leads to overexpression of HER2 benefit from HER2-targeted therapies such as trastuzumab and pertuzumab, as well as women whose breast cancers express the estrogen and progesterone hormone receptors, benefit from anti-hormone therapies. The 10% to 15% of women, like **Lori Redmer**, whose breast cancers lack the expression of HER2, the estrogen receptor and progesterone receptor are said to have triple-negative breast cancer, and for them there is no molecularly targeted therapy currently available.

Recent innovations have propelled rapid technological advances that are making it possible to efficiently read every known component of the DNA from an individual's cancer. Capitalizing on these advances is the goal of large-scale genomic enterprises such as The Cancer Genome Atlas (TCGA) and the International Cancer Genome Consortium (ICGC). These and other similar initiatives aim to identify all of the genomic changes in many types of cancer, by comparing the DNA in a patient's normal tissue with the tumor DNA, to discover the relevant genetic alterations that drive a given cancer. This information can then be used to improve our ability to diagnose, treat and prevent this devastating disease. In addition, it promises to provide new avenues of precision treatments for patients that currently have none. Moreover, near-term expansion of the use of DNA sequencing will help uncover the mutations specific to metastases, which are likely distinct from those in the original tumors from which the metastases arise. Such analyses have great potential to reveal new approaches to treating this deadly stage of the disease where our current efforts fall short.

To date, large-scale genomic analyses have been completed for just a few types of cancer, with research into many others underway. The clear message that is emerging from these studies is that while the genetic changes being uncovered vary widely, taken together they affect only a handful of signaling networks. Further, the same networks, albeit at different junctures, are affected in different cancers (see **Fig. 20**, p. 70). This is changing the way researchers view cancers. They see them more as genetic diseases, defined not as much by where they originate—in the breast, brain, lung, liver, etc.—but by the genetic changes that are their Achilles' heels (see **Fig. 19**, p. 67). At this juncture the major challenge is to determine how to best use both our current therapies and the newly developed drugs in combination to





**Figure 20: Genomic Medicine: Finding the Trees in the Forrest.** Whole genome sequencing of three different patients (blue, red and purple) reveals many individual genetic alterations in each patient. It would be impossible to administer targeted therapies to treat each of the defects; however, when the patients' genomes are compared, three potential therapeutic targets—and thus treatment strategies—emerge.

effectively target the altered signaling networks identified by genomic analyses. Further, the goal is to make this strategy part of standard of care for the treatment and prevention of cancer.

Colorectal cancer is one of the cancers for which wholesale genomic analyses have been completed (115). Researchers examined all of the genes in pairs of normal and cancerous tissue of more than 200 patients with colorectal cancer. They found that most of the genetic alterations detected in a significant portion of the cancers affected just five signaling networks. Of note, one signaling network, called the WNT signaling pathway, was altered in nearly all of the cancers (93%), suggesting that drugs that block this pathway might benefit many patients with colorectal cancer. In addition, 5% of the cancers had extra copies of the *HER2* gene, indicating that trastuzumab and pertuzumab might be effective therapies for individuals with these cancers since they successfully treat breast and stomach cancers that harbor additional *HER2* genes. The data from this study highlight the potential that large-scale genomic technologies have for identifying new drug targets for individual cancer types, but much more work is needed if we are to deliver on this promise.

Currently, the greatest use of large-scale genomic analyses remains in the research setting, as highlighted by the work of **Joyce O'Shaughnessy, M.D.**, where it can guide the development of new cancer drugs, direct the repurposing of established

therapies to treat novel genetic aberrations and inform clinical research by assigning the most appropriate patients to the best clinical trials. To date, wholesale genomic analysis has been successfully used to guide the choice of therapy for a few patients in the research setting, suggesting the day when it becomes part of standard practice is close at hand. Clearly, these advances are an early step toward a future where most cancer treatment and prevention strategies are based on both a person's genetic makeup and the genetic makeup of their specific cancer.

If this is to become a reality, the cost of deciphering a person's genetic code and that of their particular cancer must drop even further than it has in the past decade. The cost is estimated to have



**Baylor Charles A. Sammons  
Cancer Center at Dallas  
Dallas, Texas**

- Employs 250 people.
- Treats more than 8,000 unique patients each year.
- Accommodates more than 80,000 outpatient visits each year.
- Has a clinical research program that offers more than 100 clinical trials at any one time, with close to 800 patients participating annually.



## Joyce O'Shaughnessy, M.D.

Medical oncologist specializing in breast cancer  
Baylor-Sammons Cancer Center, Texas Oncology, U.S. Oncology, Dallas, Texas

Breast cancer is, in a sense, a very hopeful disease—we have had a lot of success in treating it. But for some types of breast cancer, like metastatic triple-negative breast cancer, there remain very few effective treatment options, and we need to find ways to defeat this cancer.

One approach that I have been involved in is to use whole-genome sequencing to decipher every component of the DNA from the cancer cells of several women with metastatic triple-negative breast cancer. This allows us to identify the entirety of each woman's cancer-associated mutations, which we hope can help us point them toward a specific treatment or treatments that otherwise would not have been considered for them. The sequencing and interpretive bioinformatics for this project have been done in collaboration with the Translational Genomics Research Institute (TGen) in Phoenix.

The sequencing data that we have generated is helping us match patients with clinical trials that are testing a drug or drug combination targeting the pathway or pathways that are disrupted in their cancers. However, in most cases, the technique does not have the power to allow us to influence standard of care. Just because two patients have a particular mutation and benefit from a therapy targeting the resultant disrupted signaling pathway does not mean that all patients with triple-negative breast cancer will have the same mutation(s) and benefit from the same or similar treatments. However, these patients can allow us to generate hypotheses, which we can go on to test in a subsequent clinical trial or trials, and this has been one of the biggest things to come out of our whole-genome sequencing project.

One of the best examples of how sequencing the genome of metastatic triple-negative breast cancers has generated a hypothesis that we would never have thought of otherwise involves two women whose disease had progressed on all the standard treatment options. These two women were participating in a clinical trial testing a new agent called pegylated-SN38, which is a modified form of irinotecan, a drug used to treat colorectal cancer. Both patients responded well to this drug, and our sequencing data indicated that they both had extra copies of a known cancer-driving gene, called *KRAS*, or a gene that can activate K-Ras. This gave us the idea that *KRAS* amplification might predict a good response to pegylated-SN38. We are sequencing the cancers of all the approximately 160 patients who received pegylated-SN38 to see if responders had this genetic abnormality while non-responders did not. If this proves to be true, we would still need a large-scale prospective study before changes in standard of care could be contemplated, but this finding, in a relatively small population, has the potential to help many future triple-negative breast cancer patients.

One promising example of how data from whole-genome sequencing could potentially influence the course of a patient's care, in addition to informing clinical trials, comes from a woman whose cancer was too large to remove surgically. Whole-genome sequencing of her cancer revealed that it had extra copies of a cancer-driving gene called *BRAF*, as well as defects in one of the genes that limits signaling through a pathway known as the PI3K pathway. These data led the patient to enroll in a clinical trial testing a specific combination of drugs: One that blocks the signaling pathway involving B-RAF and one that puts the brakes on the PI3K pathway. Her response to the combination was dramatic. In just two months, her tumor went from larger than the size of a grapefruit to flat. Unfortunately, she experienced complications unrelated to the treatment and had to come off the trial, but the result holds great promise and has led to several other clinical trials testing combinations of these drug types for other women like this patient.

Our experience highlights that whole-genome sequencing can help us guide patients to promising clinical trials, and that it can lead to new hypotheses. However, to test the many hypotheses that come out of studies like ours, we need to develop new approaches to performing clinical trials. In particular, we need to be able to test different drug combinations and to assess the utility of drugs approved by the FDA for one type of cancer against other cancers. It is reasonable to consider giving a patient with a metastatic cancer harboring a defined molecular defect a drug that targets that same defect but is only approved to treat a different cancer type. We just need to convince all stakeholders, in particular the regulators and insurers, that this is the case.



fallen about 100-fold since 2002, but it remains several thousand dollars per test for a robust data set (116), which is likely too high for routine clinical use. Additionally, new storage infrastructure, bioinformatics systems and telecommunications networks will be required to manage the massive amounts of information generated by the large-scale analyses. Further, the collection and interpretation of this information to inform cancer care will only be possible if we are able to support the cost of the required infrastructure, educate the current and future workforce to understand the meaning of the data generated, assemble multidisciplinary teams of researchers and physicians, and involve the patients themselves, their caregivers, and the community.



**Translational Genomics  
Research Institute (TGen)  
Phoenix, Ariz.**

- Is a non-profit organization focused on developing earlier diagnostics and smarter treatments.
- Employs approximately 300 people.
- Collaborates with Scottsdale Healthcare in clinical trials, analyzing between 400 and 600 patient samples per month.
- Provided Arizona with a total annual economic impact of \$137.7 million in 2010\*

\*Source: <http://www.tgen.org/news/index.cfm?newsid=2017>

“History demonstrates that with a strong commitment to medical research, we can change the statistics not only for cancer patients but for many other patients as well.”

**Senator Jerry Moran (R-KS)**

**Member of the Senate Appropriations Subcommittee on Labor-HHS-Education**



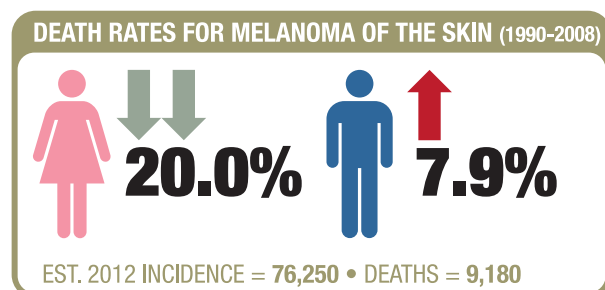


## On the Horizon

It is clear that although the altered genomes of cancer cells can have a profound effect on cancer development and spread, factors at all levels—from molecules to cells to humans—are involved. It is critical that we understand all of these influences, assimilate this knowledge and develop new ways to apply this wisdom if we are to develop comprehensive approaches to conquering cancer going forward.

At the cellular level, it will be necessary to integrate advanced genomic information with knowledge generated through the analysis of changes in the way the cancer cell's DNA is modified and packaged; this is a ripe area of research called epigenetics. The function of regions of the genome that do not encode proteins, but rather generate non-coding RNAs that fine tune the expression of proteins, will also be important to our further understanding of the biology of cancer. This comprehension must, in turn, be combined with information gleaned from studying cancer at a body-wide level through a systems biology approach that integrates our genomic and epigenomic knowledge with an understanding of the importance of metabolism (at a cellular and body-wide level) along with new knowledge of the sum of the genomes of all the microorganisms that live naturally in our bodies, collectively called the “microbiome.”

While a more comprehensive systemic understanding of cancer is critical to future near-term success, a deeper understanding of the neurological control of risky behaviors is essential to help prevent those cancers that could potentially be avoided through behavioral modification. Although progress is beginning to be made, it will take a concerted effort from all in the cancer research community to deliver on the promise of these and other forthcoming breakthroughs.



### Research at the Cellular Level: Epigenetics

The striking diversity of cell types in our body is a result of selective use of distinct parts of the genome in various kinds of cells. Information directing which parts of the DNA should be accessible in different cells of the body is conveyed by special chemical tags on the DNA called methyl groups. How the DNA is packaged with proteins into chromosomes is noted by other special chemical marks. The science of epigenetics examines how these DNA marks and packaging arise, how they affect cellular function, and how they are changed over time during normal development and in disease states such as cancer.

Most cancer cells exhibit profound abnormalities in the patterns of epigenetic marks across the genome, the sum of which is called the epigenome. In many cases, these defects work in conjunction with genetic mutations to promote the cancerous behaviors of cells. Efforts are currently underway to map these changes in all major types of cancer. We are finding that cancer epigenomes can be used to define new subtypes of cancer and can serve as indicators of patient outcome or predictors of therapeutic response. Early studies indicate that we will be able to develop sensitive assays for abnormal epigenetic marks that can be used for early detection of cancer and for assistance in monitoring drug response.

One of the exciting aspects of this research is that epigenetic abnormalities are reversible. As a result, scientists are exploring whether novel therapies that work by reversing epigenetic defects can be used to treat cancer. This concept has led to an exciting new avenue of attack on cancer, evidenced by some patients who were previously nonresponsive to traditional chemotherapy and who are now showing dramatic responses to the four FDA-approved epigenetic drugs. With cancer epigenomic profiles rapidly being assembled and drugs being developed for an ever-increasing number of epigenetic marks, it seems clear that the relatively new field of cancer epigenetics and epigenomics is destined to have a profoundly positive effect on patients in the near future and for years to come.

## Metabolomics: From Molecules to Cells to Humans

Metabolomics is the simultaneous study of hundreds to thousands of small molecules in a biological system of interest, such as the blood, urine or a tissue sample. Metabolomics provides an integrated view of how messages from the genome, epigenome and environment influence the biochemistry of a particular system at one point in time. As such, we can simultaneously measure entire biochemical pathways, such as all of the molecules that comprise the system for energy generation in a cell (and the flux through that pathway); interactive pathways, such as the pathways involved in cell growth; and conceptually linked systems, such as antioxidants and oxidative damage products. Therefore, metabolomics complements other large-scale approaches, such as genomics, epigenomics, transcriptomics and proteomics, for analyzing a cell and an individual's status at any moment in time.

Because tumor cell physiology can be different from the physiology of normal cells, it is widely anticipated that metabolomics can be used to improve our understanding of the causes of cancer, improve early diagnosis and facilitate cancer drug development. For example, investigators are examining the utility of metabolomics in identifying indicators, or biomarkers, of increased cancer risk and in establishing biomarkers that can help predict a patient's disease course or treatment response. In addition, metabolomics can be used to determine new potential drug targets and to help understand how a drug works or causes its side effects. This area of research is a rapidly growing field that shows tremendous promise for improving our understanding of cancer as well as its prevention, detection, diagnosis and treatment while simultaneously lowering the costs of both patient care and drug development.

## Whole Body Influences: The Microbiome

It is becoming increasingly clear that the many millions of microorganisms that live naturally inside or on our bodies, in areas such as the skin and the gut, have effects that resonate throughout the body. Most of the time, these microorganisms are our partners in health, contributing to a strong immune system and the digestion of dietary components to produce essential nutrients, among many other things. However, growing evidence indicates that, under certain conditions, some of these microorganisms may, in fact, worsen our health or increase our risk of certain diseases, including cancer.

These are early days in this field, however, and researchers are still trying to fully establish the nature of these microorganisms and their associated effects. One systematic approach to clarify the ambiguity involves cataloging all of the genomes of all of the microorganisms that live in or on healthy humans and those with certain diseases. The sum of all of the genomes of all these microorganisms is called "the microbiome," and it is hoped that by understanding how it changes over time as we can now do for

whole genomes, it might be possible to gain new insight into risk factors for many different human diseases, including cancer. Armed with this knowledge, it would be possible to develop new approaches to cancer prevention, detection, diagnosis and treatment. While the translation of this vision into useful clinical tools will take time, it is important that we continue providing the resources necessary for the large-scale enterprise of defining the human microbiome, given its apparent importance in human health and disease.

## Integrating Everything: Systems Biology

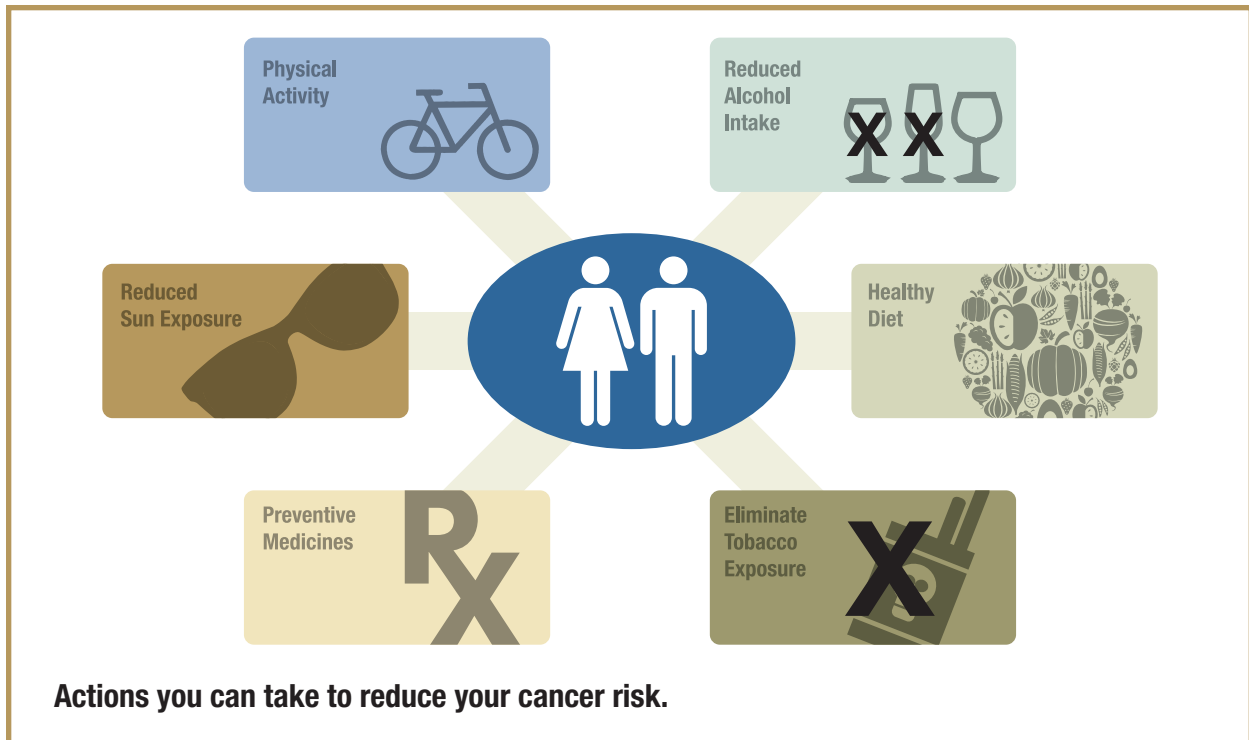
Systems biology is focused on the identification of key networks, pathways within these networks and interactions among networks that cells use to function normally. Likewise, systems biology seeks to define how these same networks are altered in cancer to support its initiation and development.

By allowing us to understand as a whole the complex systems that are created by cancer genomes, epigenomes, microbiomes and metabolomes, systems biology is helping to identify the unique growth and survival dependencies in cancer cells. It is also enabling us to predict the reserve pathways that cancers may use when initially challenged by an effective therapy. All this information is pivotal to identifying new targets for cancer medicines and novel combinations of therapies that can hit both the cancer's initial point of vulnerability and the pathways that tumor cells may use to develop drug resistance.

Unfortunately, some of the dependencies being revealed by systems biology point to drug targets that are unfamiliar to the traditional drug discovery process. Some people even refer to such targets as "undruggable." However, this view is beginning to melt away, as advances in the field of chemical biology are revealing new solutions; thus, it is clear that systems biology, in combination with other emerging areas of research, like chemical biology, can produce new approaches to cancer prevention, detection, diagnosis and treatment in the not-too-distant future.

## Improving Knowledge Application: Nanotechnology

Nanotechnology refers to the manufacturing of objects with dimensions one million times smaller than a millimeter (the smallest width of a human hair is 0.017 millimeters). Nanomedicine is the application of nanotechnology to the research and practice of medicine. Nanodrugs typically comprise a pharmaceutical agent encapsulated within a nanoparticle, with surface modifications that allow for reduced capture by the body's defenses. Nanodrugs are often characterized by increased circulatory life and enhanced concentration at the site of a targeted cancer cell to increase effectiveness and/or reduce toxicities. There are now more than a dozen nanodrugs being used for the treatment of cancer, including the breast cancer drug paclitaxel (Abraxane), and it is clear that this approach to drug delivery will become increasingly common in the future. In fact, in August of 2012, the FDA approved the latest



cancer nanodrug, vincristine sulfate liposomes (Marqibo), for the treatment of a rare, rapidly progressing form of leukemia.

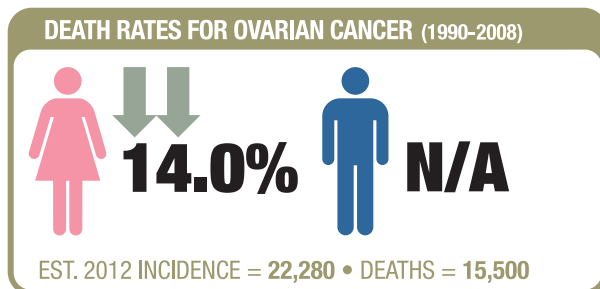
Nanotechnology is applied not only for cancer treatment, but also for cancer detection and diagnosis. Several nanotechnology based laboratory platforms are emerging; they offer opportunities for novel and improved methods for the early detection of cancer from biological fluids, the identification of novel biomarkers and the development of tests to rapidly determine the effectiveness of therapeutic regimens in individual patients. In addition, nanotechnology can be used to improve the quality of life of cancer patients. For example, there are now nanotechnology based implants that can release cancer treatments in an optimized time-release fashion to maximize the therapeutic effects of a drug, while reducing side effects and without confining patients to the hospital.

Nanotechnology holds the promise of providing a complete spectrum of tools to improve our approaches to cancer prevention, detection, diagnosis and treatment as well as to enhance quality of life.

### Reducing Cancer Risk Through Behavioral Modification

It is clear that approximately 50% of cancers could be prevented by behavioral changes such as quitting smoking, increasing exercising, adopting a more healthful diet and following recommended screening guidelines. Individuals are often aware of the negative consequences of their behaviors, but find it extremely difficult to change them. Research in affective and cognitive neuroscience is beginning to show that this is not the consequence of moral weakness. Neurobiological changes induced by behavioral addictions, such as cigarette smoking and compulsive overeating, can bias our decision-making processes and prevent us from adopting healthier lifestyles. For example, brain-imaging studies have demonstrated that nicotine, like other substances of abuse, hijacks brain circuits underlying emotional and cognitive processes. In fact, recent studies suggest that, for some individuals, cigarette smoking might reduce their ability to enjoy other pleasurable activities, making it more difficult for them to quit.

As our understanding of the neurobiological processes underlying specific behaviors increases, it might be possible, for example, to develop new personalized smoking cessation interventions that will minimize the risk of relapse and will allow smokers to achieve their goal of a smoke-free life. By discovering biomarkers that will refine diagnoses, and by creating interventions that will help individuals adopt and maintain healthy behaviors, continued and increased neuroscience research can significantly contribute to reducing cancer risk, incidence and mortality.





## Evan Lindberg

June 3, 2003 – Oct. 22, 2010  
Germantown, Md.

A message from **Wendy and Gavin Lindberg**, Evan's parents.

*"Evan has a very rare, very aggressive pediatric cancer called neuroblastoma. There is no guarantee of success with any course of treatment. We will do the best we can, but you should prepare for a very long and difficult journey."*

Those were the words of the pediatric oncologist who diagnosed our only child Evan with stage IV neuroblastoma in 2006. Evan was three years old. The phrase "long and difficult journey" does not even begin to describe what Evan endured over the course of the next four years.

Neuroblastoma is a cancer of the sympathetic nervous system that primarily strikes young children before the age of 5. Approximately 700 cases a year are diagnosed in the U.S. Evan's disease classification was the worst of the worst—stage IV, with amplification of the *N-myc* gene. Fewer than 40% of children with this specific diagnosis survive for longer than five years.

With the shock of diagnosis still overwhelming, we set out to find the treatment plan that would give Evan the best chance. We quickly learned that opinions varied widely on this subject, particularly among the experts. With no definitive cure, we were left to make the hard choices. We were constantly searching for the magic bullet that would put an end to our nightmare. Of course, there were no magic bullets, particularly after Evan relapsed less than a year into treatment.

Phase I and Phase II clinical trials became our standard of care as we tried to beat back Evan's cancer while maintaining some quality of life. "Home" became one of three places: Children's National Medical Center in Washington, D.C., Memorial Sloan-Kettering Cancer Center in New York and Children's Hospital of Philadelphia. All totaled, Evan relapsed seven times, five of which were in the brain. Each time, he amazed us and his doctors with his resolve to keep going.

No child should ever have to endure what our son endured: seven surgeries, over 150 toxic chemotherapy treatments, 25 excruciatingly painful courses of immunotherapy, months of intense radiation therapy and an endless stream of CTs, MRIs, bone scans, blood draws, shots and other grueling procedures, all resulting in over 100 nights in the hospital. Pain, nausea and discomfort were constant companions. Toughness and resolve were Evan's response.

One treatment in particular stands out: 3F8, an immunotherapy that he received at Memorial Sloan-Kettering Cancer Center. "Controlled torture" is one way to describe this antibody treatment that left Evan screaming in pain for 30 minutes, until his "rescue" narcotics kicked in and he passed out. The rest of the day was a mixture of lingering pain and lethargy until we returned the next morning to do it all again.

Evan's story is important because it reminds us of the urgency that is needed in the fight against pediatric cancer. While five-year survival rates for children with cancer (age 0 to 14 years) approach 80%, there are certain pediatric cancers, such as neuroblastoma, where the survival rates are very poor. Therefore, we call on Congress to provide the resources necessary to the National Cancer Institute to remove cancer as the leading cause of death from disease among children.

Although we lost Evan to neuroblastoma in October of 2010, neuroblastoma did not define him. Neuroblastoma never stood a chance with Evan. He survives in the hearts of everyone he met. It is in Evan's memory that we have dedicated ourselves to finding better treatments and a cure for this devastating disease. To learn more, please visit Evan's Victory Against Neuroblastoma Foundation, at [www.theevanfoundation.org](http://www.theevanfoundation.org)





# What Is Required for Continued Progress Against Cancer?

Unquestionably, we stand at a defining moment in our Nation's ability to conquer cancer. The explosion of new knowledge and the exciting technological advances, along with our ever-increasing understanding of how to apply them, are providing innovative ways to reduce the global burden of cancer. Novel strategies for making further strides in cancer prevention, detection, diagnosis and treatment are now on the horizon. Despite these opportunities, there are many challenges that must be overcome if we are to make a quantum leap forward in our mission to prevent and cure all cancers.

First and foremost, we must 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 molecules to cells to humans. We need the complete picture of what is happening within cancer cells at the level of genetics and epigenetics, as well as an understanding of the contributions of other cells in the tumor and its microenvironment. Beyond studying these in isolation, an integrated assessment—generated by the approach known as systems biology—of the tumor and the patient's response to the tumor is essential to fully understand and contextualize the cancer's causes, prognosis, vulnerabilities and responses to treatments.

With this comprehensive knowledge in hand, we can build better tools for, and be smarter in, our approaches to preventing, detecting, diagnosing and treating cancer. This vision will require a great deal of innovation, effort and collaboration from all those who care about saving lives from cancer and it will require adequate funding from the federal government and other sources to meet the challenges ahead. We must continue to push forward together, or we risk losing more people like seven-year-old **Evan Lindberg**, to this dreadful disease.

It is through research that we advance our understanding of the biological factors involved in cancer. But how we conduct research matters, and increased efforts in strategic areas are necessary to achieve a more efficient cancer research enterprise. Gaining a comprehensive picture of cancer will require new tools, new analytics, new ways of thinking and new ways of working together. These areas, which are described below, span the continuum from improvements in fundamental research to performing clinical



## Children's National Medical Center

Washington, DC

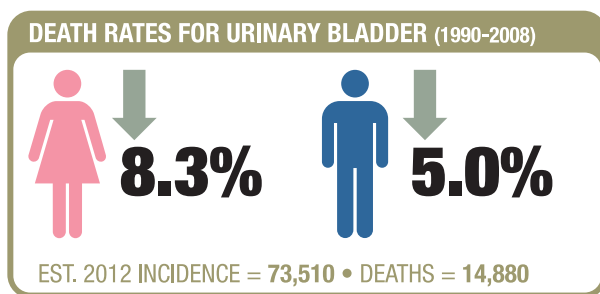
- Is a member of the Children's Oncology Group (COG) Phase I Consortium
- Assesses and/or cares for more than 360,000 patients each year.
- Assesses and cares for about 225 newly diagnosed cancer patients each year.
- Provided more than \$100 million in Community Benefit services in 2011.

research using our healthcare delivery system as a natural laboratory in which research can continue in everyday patient-clinician interactions.

## Improved Biospecimen Collection and Repository System

Biospecimens, such as samples of tumors that have been removed from cancer patients, are the backbone of cancer research. A great deal of the current understanding of cancer biology comes from studying the differences between tumor tissue and healthy tissue, between primary tumors and metastases and among different types of tumors. In this way, researchers are able to identify weaknesses to be exploited to potentially kill cancer cells.

Many research questions do not require direct access to patients and can be studied using the patients' donated biospecimens. If a repository of samples, sometimes referred to as a "biobank" or a "biorepository," is available to researchers, then hundreds or even thousands of samples can be tested quite rapidly. The utility of research on archival tissue is highlighted by the fact that this strategy has already led to a number of scientific discoveries, including the identification of HCV and the determination that HIV originates from a precursor Simian immunodeficiency virus (SIV), among others. The examination of biospecimens from clinical trial participants is also a promising means to identify drug resistance mechanisms, the knowledge of which can lead to the development of new drugs to overcome such resistance.



Currently, most biospecimens are collected and stored by a variety of institutions, organizations or individual researchers, making them inaccessible to the greater research community. Broader access to the samples would increase their value and accelerate subsequent discovery; this could be achieved by establishing a national repository of high-quality, clinically annotated tissue samples collected using global standards in privacy protection and archiving. Before any such repository is created, universal standards for collection, annotation, cataloging and storage must be agreed upon and adopted. Further, as research is performed using these samples, it will be imperative that the results from any analyses be archived at the appropriate time(s) and identified as associated with the original sample, enhancing continued discovery and decision-making. Here, too, the development and adoption of standards for data formats and sharing must precede the generation of data sets.

Finally, due to advances in genetic testing that have made it possible to link unlabeled biospecimens to individuals, patient privacy and consent are of the utmost importance, and ethical safeguards must also be agreed upon and adopted to ensure that patients are protected.

## Multidisciplinary Team Approaches and Collaboration

Modern science and medicine has taught us that to obtain a comprehensive picture of the complex set of diseases called cancer, it will be necessary to overcome barriers to progress and explore opportunities for new knowledge, new models, and new collaborative partnerships. This means integrating scientific fields, for example immunology and cancer biology, two areas that have historically tended to function independently. It also means bringing in to the cancer research effort the non-biological disciplines, such as physical, chemical, engineering and mathematical sciences, which can provide novel insights into important material properties of cancer.

Advances in technology now allow researchers to generate vast amounts of data. The combination of huge genomic data sets with complex cancer biology has created new opportunities for understanding cancer, but it has also yielded new hurdles and scientific needs. New and more sophisticated analytical methods

are required to extract meaning from mountains of numbers and have necessitated the engagement of experts in the fields of informatics and computational biology.

For multidisciplinary teams to be effective and yield new advances against cancer, we must invest in the training of both current and future researchers so that they are able to work productively within this new team environment. Also, one of the most important things to learn is how to communicate effectively across research disciplines, each with its own jargon and scientific foci. Developing successful teamwork skills requires learning to work across disciplines and academic departments and the knowledge of how to cooperate across states, regions and continents.

Successfully translating research into effective cancer interventions requires more than just dedicated and talented researchers. Along the journey from scientific discovery to intervention is a wide variety of stakeholders, including members of academia, funders, regulators, the biotechnology and pharmaceutical industries, philanthropic organizations, patient advocacy groups and the patients themselves (see **Fig. 21**, p. 79).

One type of partnership that provides an interesting opportunity to drive future innovation and accelerate productivity while reducing the cost of research and development is precompetitive

## Public-Private Partnerships

Public-private partnerships are a form of collaboration wherein otherwise competitive entities work together because the scope or complexity of the project is too large and/or difficult for any one stakeholder to successfully accomplish alone. There are several types and models for these collaborations; generally, the types of information and products that are shared are considered to be highly valuable, but not monetizable in the shared form (135).

Some successful examples are:

- SEMATECH
- I SPY-2 TRIAL
- Myelin Repair Foundation's Accelerated Research Collaboration
- Open Source Drug Discovery Consortium
- The Structural Genomics Consortium (SGC)
- Asia Cancer Research Group
- The Human Genome Project
- The SNP and Biomarker Consortia
- Multiple Myeloma Research Consortium
- The Critical Path Institute



**Figure 21: Working Together to Save Lives.**

Future progress against cancer will require the dedicated commitment of many individuals, including 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), biotechnology and pharmaceutical industries (pills), physicians (stethoscope), diagnostics companies (notepad), funding agencies and philanthropic organizations (NIH building) and payers (health insurance card). Central to transformative advances against cancer are the patients and survivors themselves.



collaboration, which refers to the sharing of research findings that have traditionally been considered proprietary commercial assets (e.g., genomic data sets or clinical trial comparator arm data) between financially distinct companies, organizations and institutions; see **Sidebar on Public-Private Partnerships**, p. 78).

Equally important are academia-industry collaborations and public-private partnerships, such as the Structural Genomics Consortium, an open-access database of the structures of biomedically relevant proteins that includes several large pharmaceutical companies among its members and financial backers. To encourage more cooperation of this nature across the sectors, it will be necessary to provide support and encouragement, such as tax incentives, funding and/or policy changes, to those who actively participate.

Effective collaborations between regulators and those involved in the drug development process are also required to speed the delivery of new treatment approaches to patients with cancer. Among the many issues that must be resolved in the near future are regulatory policies and incentives that allow multiple companies to test investigational targeted agents as therapeutic combinations in a single clinical trial. Although these efforts have begun and several companies are moving forward in a collaborative testing of this nature, many obstacles remain to be addressed. The rapid pace of innovation in cancer science and medicine requires that there be ongoing, robust communications between the FDA and the scientific

community. This is essential to ensure the seamless integration of science into the regulatory process.

## Improved Approaches to Clinical Trials

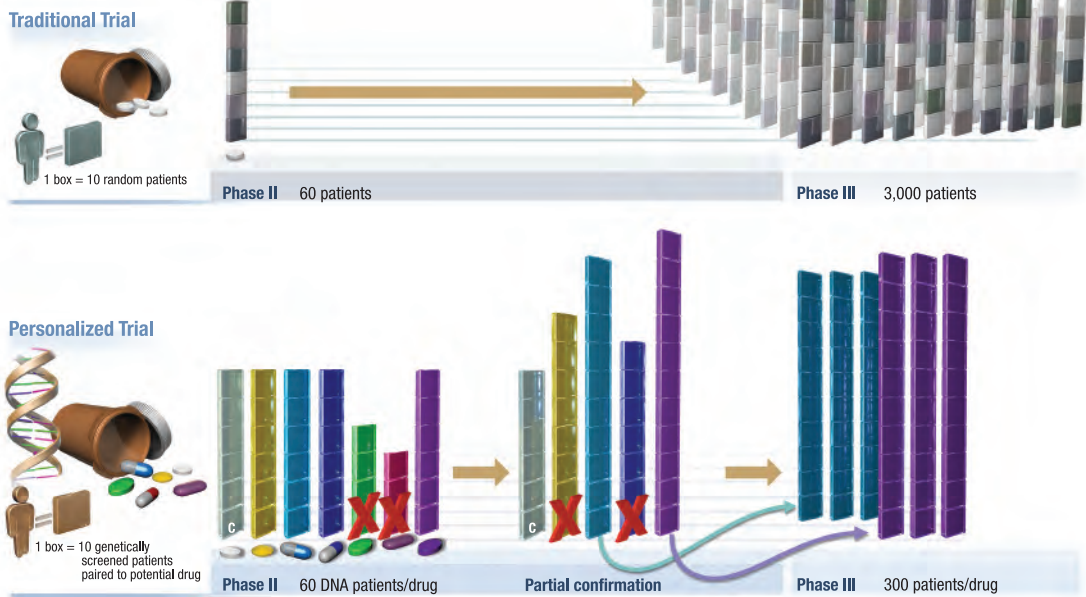
Clinical trials are a central component of cancer research, as they are the only way for therapies that show promise in laboratory studies to be translated into treatments that extend and improve the lives of cancer patients (see **Fig. 7**, p. 25). It typically takes many years for cancer clinical trials to determine the safety and efficacy of a particular treatment. If we are to accelerate this process for the benefit of cancer patients, all stakeholders (**Fig. 21**) must work together to overcome the obstacles that are preventing the conduct of faster, more efficient clinical cancer trials.

Low participation in clinical trials by adult cancer patients leads to delays in completion or even trial termination, which is a major hurdle that all clinical trials must be address. In fact, fewer than 5% of adults diagnosed with cancer participate in a clinical trial,



Fewer than **5%** of adult cancer patients participate in clinical trials.

## Molecularly Informed Clinical Trials



Cancer drug development is typically done in a series of clinical trials that expand in numbers of participants and duration, referred to as Phase I, II and III clinical trials. Phase II trials enroll small numbers of patients to test whether an investigational drug is effective at reducing tumor burden. On the other hand, Phase III trials involve very large numbers of patients and take more time to complete. These trials assume homogeneity in both the patients and the tumors; however, we now know that they are heterogeneous and multiple subpopulations exist, such as the presence of different genetic mutations. By contrast, the “Personalized Trial” approach recognizes the heterogeneous nature of the disease at the outset of the trial and the possibility that not every treatment will be effective for all patients.

In the clinical trial depicted above/below, patients are genetically screened and randomized to one of several treatments. The goal is to match experimental treatments with molecular subtypes of disease and ultimately generate “biomarker signatures.” Experimental agents are dropped early (red X) in Phase II trials if they fail to benefit patients; however, treatments that show a benefit for a particular group of patients continue to be assessed in further clinical testing. There are numerous efficiencies in this process that speed drug development, including having multiple groups simultaneously receiving investigational agents and only a single, common comparator. But the major efficiency is enabling a Phase III trial that is an order of magnitude smaller than in the traditional approach because it focuses only on the responding patient population. Two trials employing these trial designs are I-SPY 2 and BATTLE-2.

In the I-SPY 2 trial, experimental therapies are given prior to surgery, and response is determined by a series of MRI images that track tumor size. Patients are genetically screened for a number of biomarkers, and the researchers use that information to generate a common biomarker “signature” for patients who respond to a particular therapy. As the trial progresses, the experience of patients that have completed the trial is used to change the course of the trial while it is still active, rather than waiting until it has completely ended.

The BATTLE-2 trial aims to stratify advanced stage non-small-cell lung cancer patients genetically and determine outcomes in real time. This trial randomly assigns non-small-cell lung cancer patients to a targeted therapy and then follows patient response as a function of their genotype. The results of the very similarly structured, recently completed BATTLE trial suggest that this approach will be successful at linking biomarker signatures to drug response.

The BATTLE trials and the I-SPY 2 trial have given us a window into the future of cancer clinical trials. They highlight how cooperation between all stakeholders can lead to new flexible clinical trials that more efficiently and more rapidly meet the urgent needs of cancer patients. Continued collaboration is required to develop other innovative clinical trial designs that can expedite testing of new drug combinations and assess the ability of therapies to prevent metastasis.



**Disease-free survival** is the length of time a patient is in complete remission following treatment.

despite the fact that clinical trials are an opportunity to receive the newest and potentially most innovative treatments for their disease. Low participation is even more pronounced in underserved, minority and advanced-age populations, leading to concerns about the applicability of trial results to these subgroups. The reasons why patients do not participate in clinical trials include, but are not limited to, the lack of patient awareness; lack of physician awareness, encouragement or engagement in the research enterprise; fear of adverse side effects; bothersome trial requirements; ineligibility; and language or cultural barriers.

One of the greatest challenges in clinical trials is accruing enough patients to statistically prove that a given therapy has had an effect. To confirm a small, but significant therapeutic effect, a large number of patients must be enrolled in a given clinical trial to be sure that observed differences in outcomes are due to the effects of the therapy and not due to chance. Having a greater number of patients on trial translates to more time and increasing costs. One approach to accelerate the speed with which a clinical trial reaches a conclusion about the value of a new therapy is to enroll only those patients most likely to benefit from the treatment being tested. To achieve such a selective cohort, we need to identify biomarkers that predict a patient's chance of responding to the investigational therapy, such as having a mutation that will be targeted by the drug being tested. A benefit of this selective strategy is that patients unlikely to respond to the therapy will not be enrolled and, therefore, will avoid exposure to unnecessary side effects. Furthermore, trials with preselected cohorts require fewer patients because the effects of the drugs will not be averaged across responders and non-responders alike. Identifying biomarkers for subpopulations who respond is challenging, and new trial designs are being implemented to combine biomarker discovery and validation with the development of new drugs (see **Sidebar on Molecularly Informed Clinical Trials**, p. 80). Many scientific and policy issues must be considered for these new trial designs.

Another way to speed the drug development process is to reduce the length of time it takes to complete a clinical trial. The preferred endpoint used in clinical trials to determine a cancer treatment's efficacy is overall patient survival, which is often only measurable after a period of several years. As such, it can take a long time to



**Progression-free survival** is the period during which a patient does not experience any new tumor growth or cancer spread during or after treatment.

obtain definitive results of clinical trials. Surrogate endpoints that can be measured in less time than overall survival, such as progression-free survival, disease-free survival and tumor response (assessed by advanced imaging technologies, for example) are increasingly being used. To use surrogate endpoints to speed the drug development process, researchers must first prove that positive short-term surrogate endpoints actually lead to the intended long-term outcome (i.e., extended overall survival). Regulators who evaluate clinical trials must also agree on the relevance of such surrogates; therefore, interactions between clinical researchers and regulators are critical to the further development and approval of these endpoints to bring about prompt clinical trial conclusions.



**Overall survival** is the proportion of patients alive at a given time after treatment began.

### Adoption of Learning Healthcare Systems

The community that conducts cancer research and the community that implements the practical results of those findings in everyday clinical settings have all too often been poorly connected. As a result, the flow of research information can be unidirectional, from researchers to practitioners. Yet, there is much to be learned from the everyday care of patients if the appropriate data is collected about treatments and outcomes. Widespread adoption of electronic medical records (EMRs) will make it possible to more easily access and compile such clinical data. It will be essential to ensure that EMRs include standardized data fields sufficient to catalyze secondary research and foster the flow of empirical observations to drive new research questions. These data represent a previously untapped research resource and provide evidence created in settings that are representative of community care. Recently, there has been growing emphasis on reducing the separation between the research community and the clinical care community to take advantage of the vast amount of data collected during routine care to improve patient care. Care delivery systems that can actively contribute to research and improve the delivery of care are referred to as "learning healthcare systems" (see **Sidebar on Learning Healthcare Systems**, p. 29) and these will be vital to ensuring that therapies that help patients in theory actually help them in practice.

We are rapidly moving towards a future in which we understand cancer at a fundamental level. We are able to harness emerging technologies—along with new approaches of gathering, managing and interpreting the wealth of information they will provide—to achieve a world free from cancer. The U.S. could make no better choice than to continue to invest the resources needed to ensure that cancer is finally conquered for all of its citizens and the world alike.



# Investment in Cancer Research and Biomedical Science Saves Lives, Fuels Innovation and Boosts the Economy

This Report celebrates the many ways we are making research count for patients by turning scientific discoveries into better approaches for preventing, detecting, diagnosing and treating cancer. In the past 12 months alone, we can point to significant progress: continued reduction in the overall cancer death rate; forward strides in cancer prevention, including FDA approval of one new drug for cancer prevention; critical advances in cancer treatment, including eight new drugs for cancer treatment and four new uses of previously approved drugs; and the beginnings of integration of whole-genome sequencing in the clinic, which promises to change the practice of oncology. In addition, scientists at institutions in every single state across the Nation reported a myriad of basic science discoveries that are revealing novel, unanticipated insights that may well offer the keys to the next major advances for cancer patients.

## NIH Is the Catalyst for Progress Against Cancer

The NIH is one of the most important enterprises of this Nation. It is responsible for seeking fundamental knowledge about the nature and behavior of living systems and the application of that knowledge enhances public health, lengthens life, reduces the burden of illness and disability and saves lives. It does this by supporting exceptional scientists and clinicians at more than 3,000 universities, medical schools, medical centers, teaching hospitals, small businesses and research institutions across the country. In fact, more than \$25B (80%) of its \$30B budget is provided to these independent researchers who are working in communities in every state.



Federal investments of **\$3.8 billion** into the 15-year Human Genome Project generated as much as **\$796 billion**, raised personal income by **\$244 billion** and created as many as **310,000** jobs.

Core to the NIH's mission and essential to the entire cancer research ecosystem is the fundamental research that it supports. While industry is willing to invest in late-stage research to bring advances in scientific understanding to commercial realization, only the federal government can fund the basic research that marks the beginning of the pipeline (**Fig. 22**, p. 83). Industry-sponsored R&D is rightfully performed with a near-term financial return in mind, but at the NIH the returns are measured in lives both saved and improved with benefits accruing over a longer time span.

Cancer research is primarily funded through the NCI, one of the 27 institutes and centers that make up the NIH. During its 40-year history, NCI-funded research has driven significant advances in the understanding of cancer and our ability to prevent, detect, diagnose and treat it. In addition, NIH- and NCI-supported research has spurred advances in health care that have significantly reduced the burden of cancer and transformed the lives of a growing number of cancer patients, the 13.7 million cancer survivors in the U.S. alone. This remarkable progress would not have been possible without the long-standing, bipartisan commitment of our nation's policymakers to invest in research through the NIH (see **Sidebar on The NIH**, p. 83).

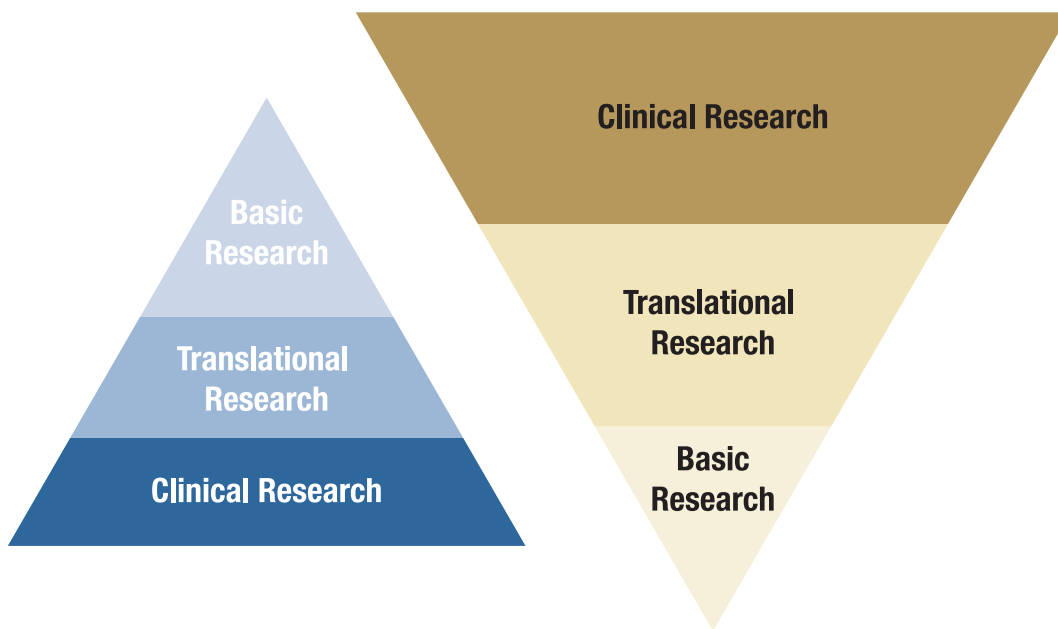
While the NIH does not attempt to realize a financial return from the research it funds, it does in fact generate significant financial

"I believe that for every dollar we spend in biomedical research through NIH, through the states and through private organizations, we get a ten-fold return — and probably more than that. It's the beginning. It's catalyst for much more. I think you will see much more of that in the future."

**Senator Richard Shelby (R-AL)**

Ranking Member on the Senate Appropriations Subcommittee on Labor-HHS-Ed





**Figure 22: The Public and Private Sectors Invest Heavily, but Differently, in Biomedical Research.** The biotechnology and pharmaceutical industry invests 40% more than the NIH in biomedical research. However, little of this investment is made in basic research, because the private sector business model requires rapid returns on its investments in order to remain viable. In contrast, the NIH dedicates more than 50% of its budget to fund basic research, which informs the translational and clinical research performed by the private sector. Continued complementary investments by both sectors are required for continued success.

returns. Thirty years ago, the Bayh–Dole Act was passed, allowing universities and investigators to lay claim to intellectual property developed using federal research dollars. This has helped spawn the multibillion dollar biotech sector, where entrepreneurial researchers have created companies from their discoveries, adding high-skilled jobs and creating new industries as a direct result of federal research investments which aid in moving basic findings to effective treatments in the clinic.

One of the most paradigm-shifting federally funded biomedical research projects in the past 20 years was the Human Genome Project, which serves as a case study in how research investments generate significant financial and societal returns. Much as NASA’s lunar mission spurred rapid advances in communications and aeronautics that quickly opened new doors to widespread use of associated technologies, the sequencing of the genome has fundamentally changed the way we think about human health and enabled entirely new approaches to research. Analysis of the 15-year, \$3.8-billion project indicated that the investment resulted in as much as \$796 billion in associated economic activity and raised personal income by \$244 billion. In 2010, as many as 310,000 jobs owed their existence to the effects of this project (117). The information and technologies emerging from the Human Genome Project radically changed researchers’ approaches to studying cancer, a disease driven by genetic abnormalities, and as a result the pace of progress has been accelerated dramatically.

## The NIH

The NIH is the leading supporter of biomedical research in the world, research that improves human health. Thanks in large part to NIH research, the average life expectancy in the U.S. today is nearly age 79, almost 30 years longer than it was in 1900, and the proportion of older people with chronic disabilities has dropped by nearly 1/3 over the past 25 years.

The NIH is comprised of 27 research-focused institutes and centers, including the NCI, which is the largest single NIH institute. Research at these institutes and centers, called intramural research, accounts for approximately 11% of the NIH budget and involves nearly 6,000 researchers and staff, in addition to 5,000 trainees.

More than 80% of the NIH budget is competitively awarded to researchers as extramural research grants, rigorously peer reviewed for relevance and scientific and technical merit.

NIH funding generates scientific discoveries and fuels new economic activity and employment in the communities that receive its funds. NIH funds support the work of more than 432,000 researchers and research personnel at more than 3,000 universities, medical schools, medical centers, teaching hospitals, small businesses and research institutions in every state.

In 2011, NIH research funding created 432,094 jobs and generated \$62.13 billion in new economic activity across the country.

# THE NIH

The NIH has lost **\$6.3 billion** from its budget over the last decade. (calculated using the Biomedical Research and Development Price Index (BRDPI), FY2003-present)

## Dwindling Research Budget and Threats of Drastic Cuts Threaten Progress for Patients, Economy

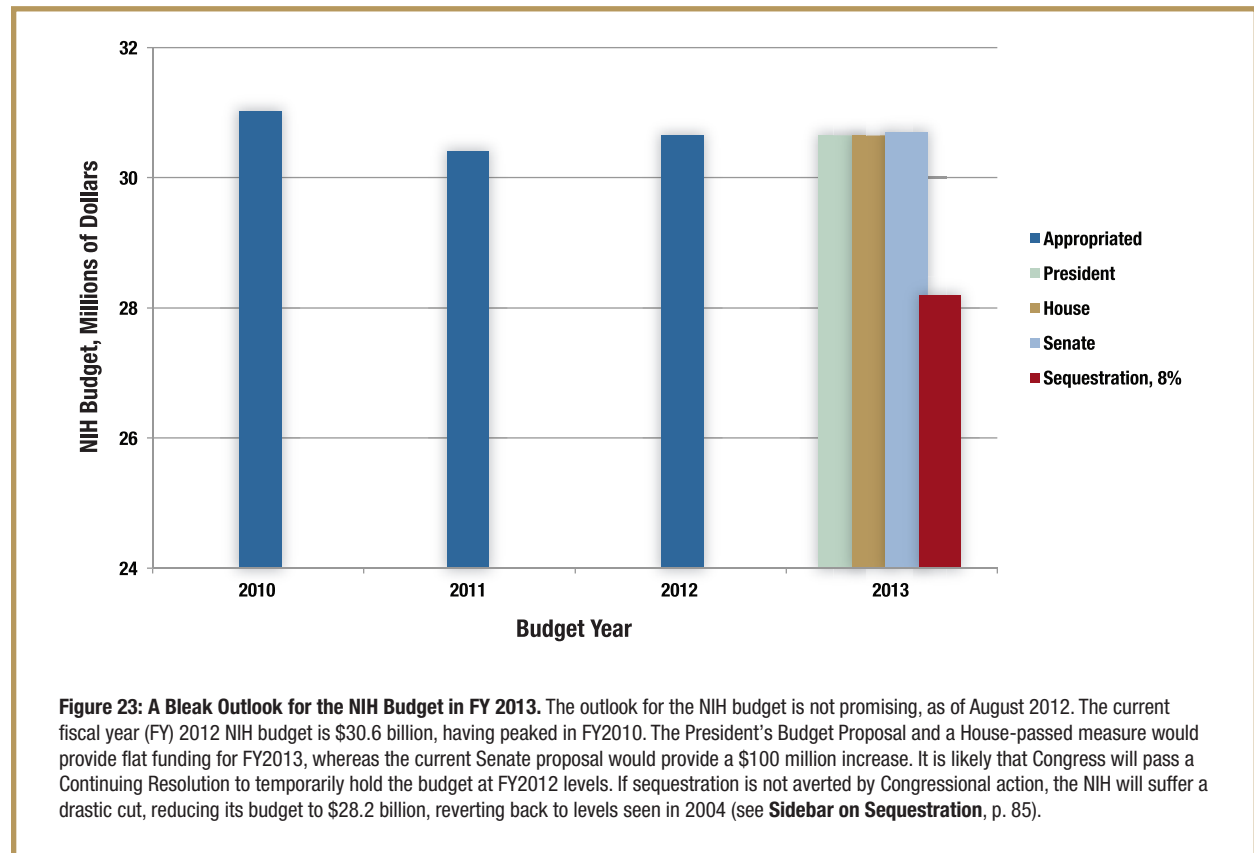
Most federally funded research projects are not as large as the Human Genome Project, and the estimated 141-fold return on investment is hard to match, but in the aggregate the \$30 billion of NIH-sponsored research in 2010 is estimated to have supported close to a half a million jobs and to have spawned an additional \$69 billion in economic activity (118). As our Nation seeks to recover from a long recession and a period of high unemployment, cutting funding to a proven economic generator is simply poor fiscal policy.

Some research advances have led to new interventions that can balance rising health care costs by avoiding needless treatments. One such technology is FDG-PET imaging, which improves staging and reduces unnecessary surgeries for Hodgkin’s disease (119). Another example is molecular diagnostic tests that predict which patients are unlikely to suffer a cancer recurrence and can safely forego costly treatment (120). Continued application of our growing knowledge will undoubtedly expand on these examples and provide additional opportunities for cost savings and improved health.

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 both America’s health and prosperity, and supporting these agencies should remain a top priority. However, in practical terms, the NIH budget has been steadily shrinking since 2003 due to biomedical inflation (Fig. 23). In fact, the NIH has lost nearly 20% of its ability to fund live-saving research over the past decade.

While the erosion of the NIH budget has been a slow and chronic problem, we face an acute challenge as 2013 begins. Because of budgetary deficits, an automatic budget-cutting action known as a “sequester” (see **Sidebar on Sequestration** p. 85) will occur beginning on January 2, 2013 if Congress does not take action to avert this crisis. The sequestration is slated to cut all federal discretionary budgets, which includes the NIH, by approximately 8%. A cut of this magnitude would have an adverse effect on every aspect of the NIH, sparing no Institute, Center or program from an immediate substantial reduction in funding.

In testimony before Congress, NIH Director Francis Collins, M.D., Ph.D. described sequestration’s effect on the NIH as potentially





## Sequestration Would Set-Back Cancer Research and Impede Medical Progress

If Congress fails to act, funding for the NIH will be cut by about \$2.4 billion or approximately 8% in January 2013 as a result of the automatic across-the-board cuts (or sequestration) required by the Budget Control Act of 2011. The estimated cut for NCI alone is \$396 million. These cuts would be *in addition* to any reductions made in the regular funding process for fiscal year 2013.

A cut of this magnitude would, according to NIH Director Francis Collins, adversely affect every aspect of the agency's work and would be particularly difficult for first-time investigators. A report by Sen. Tom Harkin, chairman of the Senate Appropriations Subcommittee on Labor, Health and Human Services, and Education warned that these cuts would mean missed opportunities for scientific discovery that could lead to improvements in human health (136). HHS expressed deep concerns that the cuts would "limit the Department's ability to accelerate scientific knowledge and innovation (137).

### Impact of an NIH and NCI Sequester

	NIH	NCI
Current Funding level	\$30.6 billion	\$5.07 billion
2013 across-the-board cut (7.8% )	-\$2.4 billion	-\$396 million
Potential 2013 level	\$28.2 billion	\$4.674 billion
Potential Reductions in NIH grants	-2,300	-300
Potential U.S. Job loss	-33,000	-5,500
Reduced economic activity	-\$4.5 billion	-\$740 million

For information on the current status of NIH funding go to: [www.cancerprogressreport.org/FederalFunding.aspx](http://www.cancerprogressreport.org/FederalFunding.aspx)

"devastating," adding that if this occurred "2,300 grants that NIH had planned to fund could not be awarded." In addition, Dr. Collins said that this would result in success rates falling to historically low levels and would be devastating for many investigators, particularly first-time investigators who are seeking to get their programs up and running.

What is so concerning is that this threat of draconian cuts to the NIH is occurring at a time where the potential for acceleration of discoveries in cancer research have never been greater. Federal investments in basic research have enabled the Nation's scientists to build upon each other's work and make substantial progress in preventing, detecting, diagnosing and treating cancer, but the prospect of significant cuts threatens to undercut this momentum.

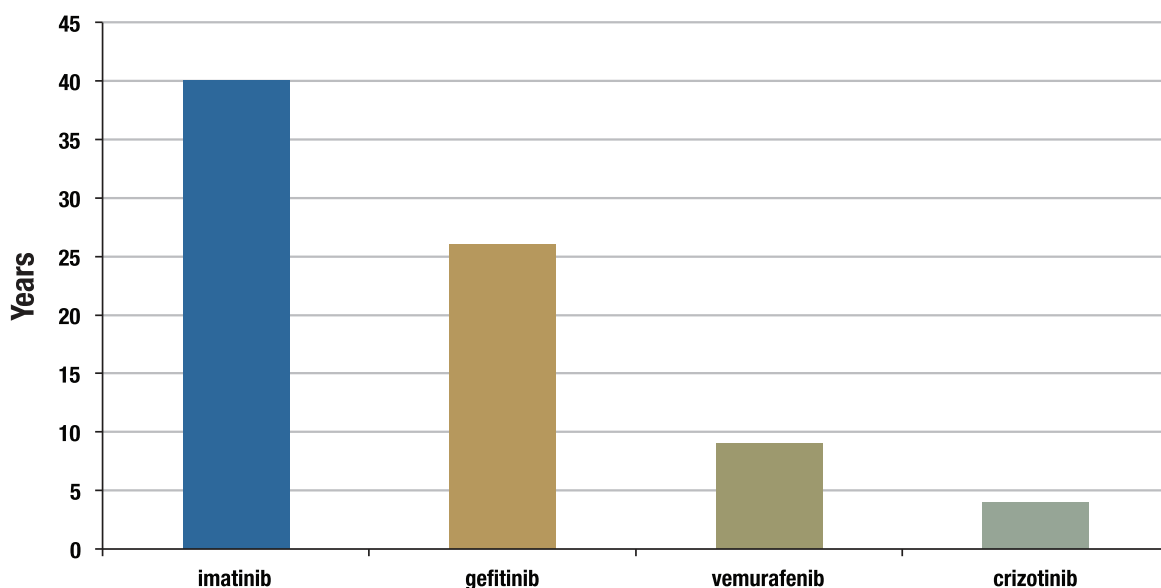
The initial scientific breakthrough that ultimately led to the cancer chemotherapeutic drug imatinib occurred in the 1950s, but with the available technology and understanding available at that time, it took 40 years to convert that basic science discovery into a life-saving treatment. Today, thanks to the knowledge that research has provided about both normal and cancer cell biology, as well as advances in technology, the time from basic discovery to an effective treatment is now much shorter. For example, the development and FDA approval of two recent targeted cancer drugs approved in 2011, took as little as nine and four years (**Fig. 24 p. 86**). Reduced funding in this era would also mean arrested and abandoned research (see **Sidebar on Sequestration**) when we are best able to reap the benefits of our prior investments.

"I think the biggest innovations of the 21st century will be at the intersection of biology and technology. A new era is beginning."

### Steve Jobs

Founder of Apple, Inc.





**Figure 24: The More We Know, the Faster We Go.** As we have continued to amass knowledge about the inner workings of cancer and technologies improve and are developed, less time is required to develop new targeted therapies. In 1960, the BCR-Abl chromosomal translocation in CML was first discovered. Because the necessary technologies and other fundamental knowledge were not yet in place, it took over 40 years to develop and approve the first targeted agent, imatinib (Gleevec), which targets BCR-Abl. In 1978, overactive EGFR signaling was associated with a subtype of lung cancer, and 26 years later, in 2004, the EGFR-inhibitor, gefitinib (Iressa), was FDA approved. More recently, in 2002, genome-wide screens first identified mutated B-Raf as a causative agent of nearly 50% of melanomas; the drug vemurafenib, which targets it, was approved in 2011. Finally, the discovery of an *ALK* gene alteration in about 5% of lung cancers in 2007 led to the remarkably rapid development and approval of the ALK inhibitor, crizotinib only four years later, in 2011. The time from target discovery to approval has declined appreciably due to our increasing knowledge base and technical advances. It is important to note, however, that development and approval of crizotinib had many advantages (such as jumpstarting development with a potent drug that had been previously tested in early phase trials for other indications), and clinical development times cannot be reduced much further as clinical trials are required to assess safety and efficacy steps. Adapted from (150).

Unfortunately, the decline in U.S. funding for biomedical research comes at a time when other nations are giving a higher priority to biomedical research and some are significantly increasing their overall investments in science and technology. For example, China has pledged to invest more than \$300 billion in biomedical research over the next five years (121). If current trends continue, in only a few years, Chinese investment in life science research will be double that of the U.S. A lack of commitment on the part of the U.S. to prioritize and maintain its investment in science threatens our Nation's long-standing global leadership in innovation.

The declining NIH and NCI budgets are also creating an environment where researchers face numerous disincentives to continue in, or even enter into, research careers. It means the loss of many young cancer investigators who will choose other careers instead of scientific careers because of a lack of funding. These disincentives are resulting in a loss of taxpayer-funded training and are adversely affecting the Nation's ability to maintain an optimal workforce for the future of cancer research.

Furthermore, current fiscal austerity means that the success rates for an investigator being awarded a research grant are diminished. In fact, current investigators face an all-time low in funding success rates, which has the detrimental effect of researchers proposing lower risk ideas which are often less innovative (121). This cycle creates missed opportunities to drive the science forward, slowing the translation of benefit to the patient, which as a country we cannot tolerate.

It is important to highlight that NIH funding of research across the Nation results in a local economic impact that is at least double the amount sponsored by the federal government. This multiplicative effect works in reverse as well, and the threatened sequester cut of \$2.4 billion would likely drain twice that amount from local economies. The ecosystem that produces biotech startups and new jobs would be thrown in reverse at a time when job creation is a social and economic priority.

# The AACR Call to Action

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

- Work in a constructive, bipartisan fashion to find a more balanced approach to address the federal deficit and prevent sequestration from occurring in January 2013; and
- Designate NIH and NCI as top national priorities by providing annual budget increases at least comparable to the biomedical inflation rate.

While it is imperative that Congress take action to stop the threatened sequester and once again make funding of the NIH and NCI national priorities, the responsibility is not theirs alone. As such the AACR also urges the citizens of this great Nation, who benefit from this life-saving research, to urge their respective legislators to support cancer research and biomedical science.

If we are to ultimately transform scientific discoveries into therapies that improve 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.





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**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.

**Acquired Immunodeficiency Syndrome (AIDS)** - A disease caused by the human immunodeficiency virus (HIV). People with AIDS are at an increased risk for developing certain cancers and for infections that usually occur only in individuals with a weak immune system.

**Anaplastic lymphoma receptor tyrosine kinase (ALK)** - The *ALK* gene makes the ALK protein, which is found on the surface of some cells. The protein can initiate a variety of signaling pathways, causing the cells it is found in to proliferate. The *ALK* gene is altered in several types of cancer, including some lymphomas, some neuroblastomas and some non-small cell lung carcinomas.

**Androgen** - A type of hormone that promotes the development and maintenance of male sex characteristics.

**Basal cell carcinoma** - A form of skin cancer that begins in a type of cell in the skin that produces new skin cells as old ones die off. It is the most common cancer, but it rarely metastasizes.

**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.

**Bioinformatics** - The science of using computers, databases and mathematics to organize and analyze large amounts of biological, medical and health information. Information may come from many sources, including patient statistics, tissue specimens, genetics research and clinical trials.

**Biomedical Research Inflation** - Biomedical inflation is calculated using the annual change in the Biomedical Research and Development Price Index (BRDPI), which indicates how much the NIH budget must change to maintain purchasing power. Over the last five year, 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.

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

**BRCA1/2 (Breast Cancer Resistance Genes 1 and 2)** - Genes that 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 pre-cancerous changes then later turn into cancer. These changes can be detected by the Pap test and treated to prevent the development of cancer.

**Chemoprevention** - The use of drugs, vitamins or other agents to try to reduce the risk of, or delay the development or recurrence 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 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 thousands 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 cancer develops, a growth of tissue or tumor usually begins as a non-cancerous 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.

**CTLA-4 (Cytotoxic T lymphocyte antigen-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.

**Double contrast magnetic imaging resonance (DC-MRI)** - A procedure in which radio waves and a powerful magnet linked to a computer are used to create detailed pictures of areas inside the body. These pictures can show the difference between normal and diseased tissue. Magnetic resonance imaging (MRI) makes better images of organs and soft tissue than other scanning techniques, such as computed tomography (CT) or x-ray. MRI is especially useful for imaging the brain, the spine, the soft tissue of joints and the inside of bones. DC-MRI uses repeated imaging to track the entrance of diffusible contrast agents into tissue over time.

**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.

**EGFR (Epidermal growth factor receptor)** - 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.

**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.

**Epstein-Barr virus (EBV)** - A common virus that remains dormant in most people. It causes infectious mononucleosis and has been associated with certain cancers, including Burkitt's lymphoma, immunoblastic lymphoma, and nasopharyngeal carcinoma.

**Familial adenomatous polyposis (FAP)** - An inherited condition in which numerous polyps (growths that protrude from mucous membranes) form on the inside walls of the colon and rectum. It increases the risk of colorectal cancer. Also called familial polyposis.

## G-P

**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 (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 multiforme and grade IV astrocytoma.

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

**Hedgehog signaling pathway** - This signaling pathway is a key regulator of embryo development. It gives cells information about what type of cell they should become and is particularly important for limb development. It is also active in cells in the adult. Inappropriate activation of the hedgehog signaling pathway has been implicated in the development of several types of cancers, including some brain, lung, breast, prostate and skin cancers.

**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 hepatitis B virus 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 hepatitis C virus 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's 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.

**Human immunodeficiency virus (HIV)** - The cause of acquired immunodeficiency syndrome (AIDS).

**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 (for example, warts) and other changes to cells. Infection for a long time with certain types of human papillomavirus can cause cervical cancer. Human papillomavirus 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.

**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.

**Janus kinases (JAKs)** - A family of proteins that work inside cells, in particular blood cells, including those of the immune system, to send signals that direct cell proliferation and survival.

**KRAS** - The *KRAS* gene makes the KRAS protein, which is involved in cell signaling pathways, cell growth, and apoptosis (cell death), may cause cancer when mutated (changed). Agents that block the activity of the mutated *KRAS* gene or its protein product may stop the growth of cancer.

**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.

**Lesion** - An area of abnormal tissue. A lesion may be benign (not cancer) or malignant (cancer).

**Lumpectomy** - Surgery to remove abnormal tissue or cancer from the breast and a small amount of normal tissue around it. It is a type of breast-sparing surgery.

**Lymphatic vessels (system)** - The tissues and organs that produce, store, and carry white blood cells that fight infections and other diseases. This system includes the bone marrow, spleen, thymus, lymph nodes, and lymphatic vessels (a network of thin tubes that carry lymph and white blood cells). Lymphatic vessels branch, like blood vessels, into all the tissues of the body.

**mTOR (Mammalian Target of Rapamycin)** - 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 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 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.

**Microbiome** - A microbiome is the totality of the genomes of all of the microorganisms in a defined environment. The human body contains over 10 times more microorganisms than human cells.

**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.

**National Cancer Institute (NCI)** - The largest of the 27 research-focused institutes and centers of the National Institutes of Health. The NCI coordinates the National Cancer Program, which conducts and supports research, training, health information dissemination and other programs with respect to the cause, diagnosis, prevention and treatment of cancer, rehabilitation from cancer, and the continuing care of cancer patients and the families of cancer patients.

**Neuroblastoma** - A type of cancer that starts in immature nerve cells affects mostly infants and children. Most neuroblastomas begin in the abdomen in the adrenal gland or next to the spinal cord, or in the chest.

**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.

**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.

**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.

**Pancreatic neuroendocrine tumor** - A rare cancer that forms in the islets of Langerhans cells (a type of cell found in the pancreas). Also called islet cell carcinoma.

**Peripheral neuropathy** - damage to nerves of the peripheral nervous system as a result of any one of numerous things, including trauma and exposure to some of the cytotoxic chemotherapies used to treat cancer. Symptoms depend on the type of nerves affected, but numbness, loss of sensation and pain in the hands and feet are common.

**Philadelphia chromosome** - An abnormality of chromosome 22 in which part of chromosome 9 is transferred to it. Bone marrow cells that contain the Philadelphia chromosome are often found in chronic myelogenous leukemia.

**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.

**Positron emission tomography (PET)** - A procedure in which a small amount of radioactive dye (sugar) is injected into a vein, and a scanner is used to make detailed, computerized pictures of areas inside the body where the dye travels; also called PET scan. Because cancer cells often use more glucose than normal cells, when combined with a radioactive glucose (sugar) called FDG, the pictures can be used to find cancer cells in the body, including micrometastases; this type of procedure is called FDG-PET.

**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 is a function of both past incidence and survival.

**PD1 (Programmed death-1)** - A protein on the surface of immune cells called T cells (see **T cell**). When PD1 attaches to 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 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 FDA 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.

**The Cancer Genome Atlas (TCGA)** - A project to catalogue genetic mutations responsible for cancer, started in 2005. The goal of the project is to provide systematic, comprehensive genomic characterization and sequence analysis of different types of human cancers.

**Treatment 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.

**Triple-negative breast cancer** - A form of breast cancer that lacks expression of three proteins that can be targeted to treat breast cancer: HER2 and the specific proteins, called receptors, that the hormones estrogen and progesterone attach to, the estrogen receptor and the progesterone receptor.

**Tumor** - An abnormal mass of tissue that results when cells divide more than they should or do not die when they should. Tumors may be benign (not cancer), or malignant (cancer); also called neoplasm.

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

**Tumor suppressor gene** - A type of gene that makes a protein called a tumor suppressor protein that helps control cell growth. Mutations (changes in DNA) in tumor suppressor genes may lead to cancer; also called an 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.

**VEGF (Vascular endothelial growth factor)** - 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.



Table 6A: 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	Folotylin
DNA Damaging Agents		
Approved Indication	Generic Name	Trade Name
Ovarian cancer	altretamine	Hexalen
Certain leukemias	arsenic trioxide	Trisenox
Multiple cancers	bendamustine	Treanda
Certain lymphomas; squamous cell and testicular cancers	bleomycin sulfate	Blenoxane
Certain leukemias	busulfan	Myleran; Busulfex
Breast, lung and ovarian cancers	carboplatin	Paraplatin; Paraplat
Brain tumors; certain lymphomas	carmustine	BiCNU
Multiple cancers	chlorambucil	Leukeran
Multiple cancers	cisplatin	Platinol-AQ
Multiple cancers	cyclophosphamide	Cytoxan
Melanoma; certain brain cancers	dacarbazine	DTIC-Dome
Multiple cancers	dactinomycin	Cosmegen
Certain leukemias	daunorubicin; daunomycin	Cerubidine
Multiple cancers	doxorubicin hydrochloride	Adriamycin PFS; Adriamycin RDF
Certain leukemias; breast and stomach cancers	epirubicin hydrochloride	Ellence
Prostate cancer	estramustine	Emcyt; Estracyt
Certain leukemias	idarubicin	Idamycin PFS
Multiple cancers	ifosfamide	Ifex
Colon, lung and rectal cancers	irinotecan	Camptosar; Campostar
Brain tumors	lomustine	CeeNU
Multiple cancers	mechlorethamine hydrochloride	Mustargen
Multiple cancers	melphalan	Alkeran
Certain lymphomas	methoxsalen	Uvadex
Multiple cancers	mitoxantrone	Novantrone
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	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
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
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

INCREASING PRECISION

Table 6B: FDA-Approved Monoclonal Antibodies for Oncology

Immune System Modifiers		
Approved Indication	Generic Name	Trade Name
Multiple cancers	interferon alfa-2b	Intron A
Melanoma; kidney cancer	aldesleukin	Proleukin
Myelodysplastic syndrome	lenalidomide	Revlimid
Proteasome Inhibitor		
Approved Indication	Generic Name	Trade Name
Multiple myeloma	bortezomib	Velcade
Multiple myeloma	carfilzomib	Kyprolis
Epigenetics Modifiers		
Approved Indication	Generic Name	Trade Name
Myelodysplastic syndrome	azacitidine	Vidaza
Myelodysplastic syndrome	decitabine	Dacogen
Certain lymphomas	romidepsin	Istodax
Certain lymphomas	vorinostat	Zolinza
Angiogenesis Inhibitors		
Approved Indication	Generic Name	Trade Name
Kidney cancer	axitinib	Inlyta
Kidney cancer; soft tissue sarcomas; gastrointestinal stromal tumors	pazopanib	Votrient
Kidney cancer	sorafenib	Nexavar
Gastrointestinal stromal tumors; kidney cancer; some pancreatic cancers	sunitinib	Sutent
Thyroid cancer	vandetanib	Caprelsa
Colorectal cancer	ziv-aflibercept	Zaltrap
Cell Signaling Inhibitors		
Approved Indication	Generic Name	Trade Name
Lung cancer	crizotinib	Xalkori
Some leukemias	dasatinib	Sprycel
Some lung cancers	erlotinib	Tarceva
Some pancreatic cancers; kidney cancer; non-cancerous kidney tumors; HER2+ 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
Myelofibrosis	ruxolitinib	Jakafi
Kidney cancer	temsirolimus	Torisel; Torisel
Thyroid cancer	vandetanib	Caprelsa
Melanoma	vemurafenib	Zelboraf
Certain type of skin cancer	vismodegib	Erivedge

\*\* 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.

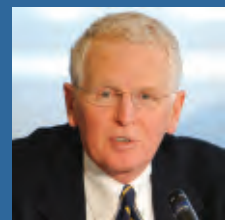
Angiogenesis Inhibitor		
Approved Indication	Generic Name	Trade Name
Colon; kidney; lung; certain brain cancers	bevacizumab	Avastin
Blood Cancer Specific		
Approved Indication	Generic Name	Trade Name
Certain leukemias	alemtuzumab	Campath
Certain lymphomas	brentuximab vedotin	Adcetris
Certain lymphomas	ibrutinomab	Zevalin
Certain leukemias	ofatumumab	Arzerra
Certain lymphomas	rituximab	Rituxan
Certain lymphomas	tositumomab I131	Bexxar
Cell Signaling Inhibitors		
Approved Indication	Generic Name	Trade Name
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	denosumab	Xgeva

INCREASING PRECISION

Table 7: Surgical and Radiotherapy Advances

<b>Surgical Advances Used to Treat</b>		<b>Procedure</b>
Breast cancer		Mastectomy
Breast cancer		Lumpectomy
Testicular cancer		Orchiectomy
Multiple head, neck and chest cancers		Video-Assisted Thoracoscopic Surgery (VATS)
Variety of abdominal cancers		Laparoscopic surgery
Sarcoma and other cancers		Reconstructive and limb-sparing surgeries
Kidney cancer		Partial nephrectomy
Pancreatic cancer		The Whipple/modified Whipple procedure
Stomach-sparing pancreatic surgery for pancreatic cancer		Pancreatodudenectomy
Rectal cancer		Total mesorectal excision
Prostate cancer		Nerve-sparing prostatectomy
Rectal cancer		Transanal Endoscopic Microsurgery (TEM)
Testicular cancer		Modified retroperitoneal lymph node dissection
Breast, melanoma, and colorectal cancers		Sentinel lymph node biopsies
Breast cancer, laryngeal cancer, and anal/rectal cancer		Neoadjuvant chemotherapy
Multiple cancers		Robotic or computer-assisted surgeries
<b>Radiotherapy Advances Used to Treat</b>		<b>Procedure</b>
Prostate, cervical, other cancers		Brachytherapy
Multiple cancers		Computer-guided radiation therapy (cyber knife)
Brain and some lung cancers		Stereotactic radio surgery (gamma knife)
Multiple cancers		Adjuvant/simultaneous radiotherapy
Head and neck cancers; prostate cancer		Intensity Modulated Radiation Therapy (IMRT)
Rectal cancer		Neoadjuvant radio/chemotherapy
Prostate cancer		Adjuvant radiotherapy
Pediatric, thoracic, and prostate cancers		Proton Therapy





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