Special Feature on Immunotherapy

AACR Cancer Progress Report 2013
Making Research Count for Patients: A Continual Pursuit

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

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

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

This report and the ongoing community-wide effort to rally support for biomedical research could not come at a more important time. Cancer research and biomedical science are facing the most serious funding crisis in decades. Since 2003, the budgets for the NIH and the NCI have been steadily shrinking because the amount of funding provided to them by Congress each year has been significantly less than what is needed to just keep pace with biomedical inflation. As a result, there has been an effective 20 percent reduction in the ability of these agencies to support lifesaving research. In addition to the gradual erosion of funding due to inflation, the NIH was forced to absorb a $1.6 billion in direct budget cuts in March 2013, under what is known as sequestration. The NCI suffered a commensurate budget cut of $293 million. As a result, the NIH is now funding the lowest number of research projects since 2001, and unless Congress takes action, sequestration will result in an overall reduction to the NIH budget of $19 billion by 2021.

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

What is worse is the fact that diminished federal investments in cancer research come at a time when the American people must need new research advances. Cancer is the second most common cause of disease-related death in the United States, exceeded only by heart disease, and it will become the number one killer in the very near future unless we are able to avert this projected increase in cancer cases through research. Cancer currently accounts for nearly one of every four disease-related deaths in the United States, and is expected to claim the lives of 580,350 Americans this year. In addition, it is estimated that 1.6 million Americans will be diagnosed with cancer this year. Globally, cancer incidence is also on the rise, and it is anticipated to claim the lives of approximately 17 million people by 2030.

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

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

Charles L. Sawyers, M.D.
AACR President
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Chief Executive Officer

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 advancement of cancer research for the benefit of cancer patients.

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

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

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

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

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Executive Summary

Background

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

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

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

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

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

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

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

Prevention and Early Detection

Many of the greatest reductions in the morbidity and mortality of cancer have resulted from advances in cancer prevention and early detection. Yet, more than 50 percent of the 580,350 cancer deaths expected to occur in the United States in 2013 will be related to preventable causes. Most notable among these causes are tobacco use, obesity, poor diet, lack of physical activity, exposure to ultraviolet radiation either through the use of tanning devices or direct sun exposure, and failure to use or comply with interventions that treat or prevent infectious causes of cancer. Modifying personal behaviors to adopt a healthier lifestyle that eliminates or reduces these risks, where possible, could therefore, have a remarkable impact on our nation’s burden of cancer. However, a great deal more research and resources are needed to understand how to best help individuals to change their lifestyle.

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

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

Making Research Count for Patients: A Continual Pursuit

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

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

There are also many cancer therapeutics showing great potential in clinical trials. One group of cancer therapeutics that are likely to revolutionize the treatment of certain cancers in the very near future, are immunotherapies. These therapeutics, which train a patient’s immune system to destroy their cancer, are yielding both remarkable and long-lasting responses. Moreover, not all immunotherapies work in the same way, and early studies indicate that combining immunotherapies that operate differently or combining immunotherapies with other radiation therapy or other drugs can enhance the benefits of these incredibly powerful cancer therapeutics.

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

What is Required for Continued Progress Against Cancer?

Bipartisan support from Congress and the administration for the NIH and NCI has enabled extraordinary progress against cancer. In doing so, it has saved countless lives, both in the United States and throughout the world, while catalyzing the development of the biotechnology industry and promoting economic growth in America. However, there are many challenges to overcome if we are to realize our goal of conquering cancer.

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

AACR Cancer Progress Report to Congress and the Administration

As we enter the third year of our effort to communicate the progress being made toward conquering cancer to Congress and the American public, we are also celebrating the many ways that we have continued to make research count for patients in the past year. Scientific momentum has brought the arrival of a new era in which we will be able to develop even more effective interventions and save more lives from cancer, but to do so will require an unwavering, bipartisan commitment from Congress and the administration to invest in our country’s remarkably productive biomedical research enterprise.

This year’s report highlights some of the most remarkable advances that are likely to revolutionize the treatment of certain cancers in the very near future, are immunotherapies. These therapeutics, which train a patient’s immune system to destroy their cancer, are yielding both remarkable and long-lasting responses. Moreover, not all immunotherapies work in the same way, and early studies indicate that combining immunotherapies that operate differently or combining immunotherapies with other radiation therapy or other drugs can enhance the benefits of these incredibly powerful cancer therapeutics.

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

The AACR Call to Action

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

• Designate NIH and NCI as national priorities by providing annual budget increases at least comparable to the biomedical inflation rate.

• Protect the NIH and NCI from another year of the insidious across-the-board budget cuts under what is known as sequestration, and reinstate the $1.6 billion in funding that NIH lost in March 2013.

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

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

A Snapshot of a Year of Progress

Thanks to Cancer Research:

From 1990 - 2012

13.7 Million Survivors

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

11 new drugs to treat a variety of cancers

3 new uses for previously approved cancer drugs

3 new imaging technologies

3 Million Survivors

1,024,400 Lives Saved!

Over 100 years of fundamental discoveries in immunology are now yielding remarkable and long-lasting patient responses through:

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

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

Tobacco use

Obesity and being overweight

Lack of physical activity

Diet poor in nutrition
The Status of Cancer in 2013

In this section you will learn:

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

Definitive Progress has Been Made Against Cancer

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

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

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

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

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

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

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

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

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

<table>
<thead>
<tr>
<th>New Drugs</th>
<th>Angiogenesis Inhibitors</th>
<th>Approved Indication</th>
<th>Generic Name</th>
<th>Trade Name</th>
<th>Formulation</th>
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<td>Thyroid cancer</td>
<td>cabozantinib</td>
<td>Cometriq</td>
<td>Formulation</td>
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<td>Colorectal cancer, gastrointestinal stromal tumors</td>
<td>regorafenib</td>
<td>Stivarga</td>
<td>Formulation</td>
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<th>New Drugs</th>
<th>Cell Cytoskeleton Modifying Agents</th>
<th>Approved Indication</th>
<th>Generic Name</th>
<th>Trade Name</th>
<th>Formulation</th>
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<td>Certain form of lung cancer*</td>
<td>paxil/mm abnormal bound particles</td>
<td>Abraxane</td>
<td>Formulation</td>
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<th>New Drugs</th>
<th>Cell Signaling Inhibitors</th>
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<th>Generic Name</th>
<th>Trade Name</th>
<th>Formulation</th>
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<td>HER2+ breast cancer</td>
<td>ado-trastuzumab emtansine</td>
<td>Kadcyla</td>
<td>Formulation</td>
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<tr>
<td>Certain type of lung cancer</td>
<td>atezolizumab</td>
<td>Tecentriq</td>
<td>Formulation</td>
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<td>Certain type of melanoma</td>
<td>dabrafenib</td>
<td>Tafinlar</td>
<td>Formulation</td>
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<td>Certain type of bone cancer*</td>
<td>denosumab</td>
<td>Xgeva</td>
<td>Formulation</td>
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<td>Certain type of leukemia</td>
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<td>Formulation</td>
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<td></td>
</tr>
<tr>
<td>Certain type of melanoma</td>
<td>trametinib</td>
<td>Mekinist</td>
<td>Formulation</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>New Drugs</th>
<th>Immune System Modifiers</th>
<th>Approved Indication</th>
<th>Generic Name</th>
<th>Trade Name</th>
<th>Formulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Certain type of lymphoma*</td>
<td>lenalidomide</td>
<td>Revlimid</td>
<td>Formulation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multiple myeloma</td>
<td>pomalidomide</td>
<td>Pomalyst</td>
<td>Formulation</td>
<td></td>
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</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>New Drugs</th>
<th>Protein Translation Inhibitor</th>
<th>Approved Indication</th>
<th>Generic Name</th>
<th>Trade Name</th>
<th>Formulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Certain type of leukemia</td>
<td>omacetaxine mepesuccinate</td>
<td>Syndo</td>
<td>Formulation</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>New Drugs</th>
<th>Radiation-emitting Drugs</th>
<th>Approved Indication</th>
<th>Generic Name</th>
<th>Trade Name</th>
<th>Formulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostate cancer bone metastases</td>
<td>radium Ra 223 dichloride</td>
<td>Xofigo</td>
<td>Formulation</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* New indication for 2013. When multiple trade names are used, only the most common have been listed.
promise because it is estimated that more than half of the cancer deaths that occur in the United States are preventable through lifestyle modifications (10).

Cancer is not unique to America; it is a global problem. Cancer incidence worldwide is predicted to increase from 12.8 million new cases in 2008 to 22.2 million in 2030 (11). Without the development of more effective preventive interventions and treatments, this will translate to more than 1.3 million lives claimed by cancer in 2030 (12).

### Table: Select Cancer Incidence, Mortality and Change in Death Rates (1990-2000)

<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>Estimated 2013 Incidence (10,000)</th>
<th>Estimated 2013 Deaths (10,000)</th>
<th>Change in Death Rate % Decreasing</th>
<th>Change in Death Rate % Increasing</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Malignant Cancers</td>
<td>1,662,390</td>
<td>580,350</td>
<td>-24.4</td>
<td>+11.8</td>
</tr>
</tbody>
</table>

* Data are rounded to the nearest 10; estimated new cases exclude basal cell and squamous cell skin cancers and in situ carcinomas except urinary bladder. † Estimated incidence and deaths for colon and rectal cancers are combined. ‡ More deaths than cases may reflect lack of specificity in recording underlying cause of death on death certificates and/or an undercount in the case estimate.

Source: Estimated new cases are based on cancer incidence rates from 49 states and the District of Columbia during 1995-2009 as reported by the North American Association of Central Cancer Registries (NAACCR), representing about 98% of the US population. Estimated deaths are based on US mortality data during 1995-2009, National Center for Health Statistics, Centers for Disease Control and Prevention.

### Cancer: An Expensive Disease.

**Biomedical Research: A Wise Investment**

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

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

In this section you will learn:

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

The Origins of Cancer

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

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

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

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

The Virtuous Cycle of Biomedical Research

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

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

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

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

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

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

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

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

Because research is an iterative cycle, regulatory approval is not the end of the line. It is vital that what happens at patients’ bedside feeds back into the research cycle.

For example, even if clinical trials indicate that an agent, drug, or tool can help reduce the burden of cancer and it is adopted into routine clinical practice, continued monitoring of its safety and benefits provides important information for improved use and further innovation.

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

Five Moleculary Targeted Therapies

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

A list of in this section topics you may find interesting:

- Cancer
- Research
- Progress
- Report 2013
- American Association for Cancer Research

Downloaded from dinccancerres.aacrjournals.org on November 1, 2017. © 2013 American Association for Cancer Research.
The molecularly targeted therapy crizotinib blocks the abnormal protein that leads to about 5 percent of non-small cell lung carcinomas, EML4-ALK.

Crizotinib

The Genetic Basis of Cancer

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

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

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

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

There are many different types of mutations that can cause cancer. These range in size from a single base change (a letter is out of order or missing) to extra copies of a gene (a paragraph is repeated many times) to the deletion of a large segment of a chromosome (part of a chapter is missing) (see Figure 6, p. 12). Further, chromosomes can break and recombine, resulting in the production of entirely new proteins, like the one that causes most cases of chronic myelogenous leukemia (CML) and the one that leads to about 5 percent of non-small cell lung carcinomas.
Over the years, researchers have determined that cancer-associated genetic mutations are most often found in one of two classes of genes: proto-oncogenes and tumor suppressor genes. These genes normally regulate the natural processes of cell growth and death to keep our tissues and organs healthy.

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

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

The understanding that cancer can be caused by genetic changes that lead to altered proteins and disruption of normal cell behaviors has spurred the development of cancer drugs that target these proteins. This approach, treating cancer patients based on the genetic and molecular profile of their cancer, is referred to as personalized cancer medicine, or precision medicine.

Beyond Genetics: The Role of Epigenetics

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

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

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

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

One of the most exciting discoveries is that some epigenetic abnormalities are reversible. As a result, researchers are exploring whether therapies that work by reversing specific epigenetic defects can be used to treat cancer. The potential of this concept is highlighted by the fact that there are already FDA-approved epigenetic drugs, which are used to successfully treat some patients with lymphoma or preleukemia who are nonresponsive to traditional chemotherapy.

Epigenetic Therapies

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

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

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

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

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Hepatitis C Virus Screening

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

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

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

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

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

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

<table>
<thead>
<tr>
<th>Approved Indication</th>
<th>Generic Name</th>
<th>Trade Name</th>
<th>Formulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kidney cancer</td>
<td>axitinib</td>
<td>Inlyta</td>
<td>9</td>
</tr>
<tr>
<td>Colon, kidney, and lung cancers</td>
<td>bevacizumab</td>
<td>Avastin</td>
<td></td>
</tr>
<tr>
<td>Kidney cancer, soft tissue sarcoma, gastrointestinal stromal tumors</td>
<td>pazopanib</td>
<td>Votrient</td>
<td></td>
</tr>
<tr>
<td>Colorectal cancer, gastrointestinal stromal tumors</td>
<td>regorafenib</td>
<td>Stivarga</td>
<td></td>
</tr>
<tr>
<td>Kidney cancer</td>
<td>sorafenib</td>
<td>Nexavar</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal stromal tumors; kidney cancer; some pancreatic cancers</td>
<td>sunitinib</td>
<td>Sutent</td>
<td></td>
</tr>
<tr>
<td>Thyroid cancer</td>
<td>vandetanib</td>
<td>Caprosa</td>
<td></td>
</tr>
<tr>
<td>Colorectal cancer</td>
<td>ziv-aflibercept</td>
<td>Caprelsa</td>
<td></td>
</tr>
</tbody>
</table>

**modified antibody**

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**Developing Cancer**

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

Metastatic disease is a dire occurrence that almost inevitably leads to death. A fundamental understanding of this process is essential to conquering cancer. Research over the past few decades has just begun to teach us why metastatic disease is so difficult to treat. To begin, metastasis is a complex, multistep process, and virtually every step can be achieved through multiple different pathways. Thus, obstructing only one pathway therapeutically is generally insufficient to stop the entire process. Compounding this problem is the fact that cancer cells can travel to other parts of the body before the initial tumor is found, and then lie dormant in this location, becoming active later years to form a metastatic tumor.

Currently, we do not know enough about cancer cell dormancy to either efficiently locate and eliminate these cells or design therapies that could prevent them from reawakening, facts that underscore the critical need for further research in these areas.

Improvements in our understanding of the development of cancer have allowed us to detect some precancerous lesions and interrupt them before they become life-threatening. For example, in the cervix, precancerous lesions are called cervical intraepithelial neoplasia. These can be detected using the Papanicolaou (Pap) test and can be removed or destroyed by several procedures including cryocautery, electrocautery, and laser cautery.

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

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

Prevention and Early Detection

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

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

Healthy Living Can Prevent Cancer

Decades of research have led to the identification of numerous factors that affect a person’s risk of developing cancer (see Figure 9). Through this work, scientists have come to the conclusion that more than 50 percent of the 580,350 cancer deaths expected to occur in the United States in 2013 will be related to preventable causes such as tobacco use, obesity, poor diet, and lack of physical activity (10). Modifying personal behaviors (see Figure 10, p. 20) to eliminate or reduce these risks, where possible, could, therefore, have a tremendous impact on our nation’s burden of cancer. Data obtained from (10).

Eliminating High-Risk Activities

Everyone could dramatically reduce their risk of certain cancers by making two changes to the ways they live: cutting out tobacco products and avoiding excessive exposure to ultraviolet (UV) light, a form of damaging radiation emitted by the sun, sunlamps, and tanning beds. Making these changes not only reduces the chances of developing certain cancers, but can also reduce cancer recurrence or improve outcomes following a cancer diagnosis.

Tobacco Use and Cancer

The scientifically established causal relationship between cigarette smoking and lung cancer was first brought to the public’s attention in 1964, when the “U.S. Surgeon General’s Report on Smoking and Health” was published (15). This report set in motion major policy changes, media campaigns,
and other measures to combat cigarette smoking in the United States (see Table 4). As a result of these efforts, the prevalence of smoking decreased from 42 percent of Americans in 1965 to 18 percent in 2012 (16). This decrease has been credited with saving millions of lives that would otherwise have been lost not only to lung cancer, but also to 17 other types of cancer directly related to tobacco use (9) (see Figure 11, p. 23).

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

Figure 10: Act Now to Reduce Your Cancer Risk. Decades of research have led to the identification of numerous factors that affect a person’s risk of developing cancer (see Figure 9, p. 19). The factors with the biggest influence on cancer risk can be eliminated or reduced by modifying personal behaviors. For example, eliminating tobacco use; eating a healthy and balanced diet; increasing physical activity; and other measures to combat cigarette smoking in the United States (see outreach efforts. While the link between smoking and disease is widely understood today, this was not always the case. Over the past 50 years numerous policies also aim to reduce smoking prevalence, particularly by discouraging youth initiation. Together, anti-smoking public policies have contributed to widespread understanding of the risks associated with tobacco use, but evidence points to the need for continued education and outreach efforts.

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

<table>
<thead>
<tr>
<th>Year</th>
<th>Policy</th>
<th>Importance</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>1964</td>
<td>First Surgeon General’s Report</td>
<td>First public declaration of the link between smoking and disease</td>
<td>EDUCATION</td>
</tr>
<tr>
<td>1965</td>
<td>Cigarette Labeling and Advertising Act</td>
<td>Requires all cigarette packs to carry health warning labels</td>
<td>WARNING</td>
</tr>
<tr>
<td>1967</td>
<td>FCC Fairness Doctrine Messages on TV and Radio</td>
<td>Requires broadcast TV and radio stations to offer time for public service announcements to counter cigarette advertising</td>
<td>EDUCATION</td>
</tr>
<tr>
<td>1971</td>
<td>Ban on cigarette advertising on TV</td>
<td>Eliminates a source of significant advertising promoting cigarette use</td>
<td>PROTECTION</td>
</tr>
<tr>
<td>1971</td>
<td>Warning labels strengthened</td>
<td>Warning labels are strengthened due to mounting evidence of the adverse health effects of smoking</td>
<td>WARNING</td>
</tr>
<tr>
<td>1975</td>
<td>The Minnesota Clean Indoor Air Act</td>
<td>First statewide law requiring separate smoking and non-smoking areas for indoor public spaces</td>
<td>PROTECTION</td>
</tr>
<tr>
<td>1983</td>
<td>Bipartisan Federal Cigarette Tax Increase to $0.16/pack</td>
<td>Price increases discourage smoking, particularly among the youth</td>
<td>$</td>
</tr>
<tr>
<td>1986</td>
<td>Surgeon General’s Report on Involuntary Exposure to Cigarette Smoke</td>
<td>Alerts the public that secondhand smoke is also harmful to health</td>
<td>EDUCATION</td>
</tr>
<tr>
<td>1988</td>
<td>Smoking banned on U.S. flights under two hours</td>
<td>Eliminates exposure of non-smokers to secondhand smoke</td>
<td>PROTECTION</td>
</tr>
<tr>
<td>1990</td>
<td>Smoking banned on all U.S. flights</td>
<td>Eliminates exposure of non-smokers to secondhand smoke</td>
<td>PROTECTION</td>
</tr>
<tr>
<td>1991-1993</td>
<td>Bipartisan Federal Cigarette Tax Increase to $0.24/pack</td>
<td>Price increases discourage smoking, particularly among the youth</td>
<td>$</td>
</tr>
<tr>
<td>1998</td>
<td>Master Settlement Agreement</td>
<td>Prohibits targeted marketing to youth and funds counter advertising campaigns</td>
<td>PROTECTION</td>
</tr>
<tr>
<td>2000</td>
<td>Smoking banned on all international flights leaving US</td>
<td>Eliminates exposure of non-smokers to secondhand smoke</td>
<td>PROTECTION</td>
</tr>
<tr>
<td>2000-2002</td>
<td>Bipartisan Federal Cigarette Tax Increase to $0.30/pack</td>
<td>Price increases discourage smoking, particularly among the youth</td>
<td>$</td>
</tr>
<tr>
<td>2009</td>
<td>Family Smoking Prevention and Tobacco Control Act</td>
<td>Bans the use of fruit flavoring in cigarettes, and give-aways like 5 dress and 50 packs</td>
<td>PROTECTION</td>
</tr>
<tr>
<td>2009</td>
<td>Family Smoking Prevention and Tobacco Control Act</td>
<td>Gives the FDA authority to regulate tobacco products for the first time in the country’s history.</td>
<td>PROTECTION</td>
</tr>
<tr>
<td>2009</td>
<td>Bipartisan Federal Cigarette Tax Increase to $1.01/pack</td>
<td>Price increases discourage smoking, particularly among the youth</td>
<td>$</td>
</tr>
<tr>
<td>2010</td>
<td>The Affordable Care Act</td>
<td>Sets aside funds for smoking prevention efforts and strengthens access to cessation treatment</td>
<td>PROTECTION</td>
</tr>
</tbody>
</table>

While the link between smoking and disease is widely understood today, this was not always the case. Over the past 50 years numerous policies also aim to reduce smoking prevalence, particularly by discouraging youth initiation. Together, anti-smoking public policies have contributed to widespread understanding of the risks associated with tobacco use, but evidence points to the need for continued education and outreach efforts.
It is not only the lives of those who use tobacco products that are at risk; scientific evidence has shown that exposure to secondhand tobacco smoke also causes cancer. This prompted the surgeon general to declare that there is no safe level of exposure to tobacco smoke (19). Although this has led to some important public health policies restricting smoking in public places (see Table 4, p. 21), smoking remains a huge threat to the public’s health (20, 21). Countless lives could be saved through continued development and implementation of effective tobacco prevention, cessation, and control strategies.

Outdoor and Indoor Tanning and Cancer

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

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

Preventing skin cancer by protecting skin from UV light exposure would not only limit the morbidity and mortality caused by these conditions, but would also save enormous amounts of money. It has been estimated that the total direct cost associated with the treatment of melanoma in 2010 was $23.36 billion in the United States (26). Given that melanoma incidence rates continue to increase (1), patients, researchers, and politicians seeking to balance their budgets need to come together to develop and implement more effective policy changes and public education campaigns to help reduce the health and economic burdens of skin cancer.

Cancer-associated Infectious Agents

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

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

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

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Sleep Disturbances and Cancer

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

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

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

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

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

Moreover, it is becoming increasingly clear that cancer incidence and outcomes are profoundly affected by excess energy reserve accumulation. Importantly, many of the factors that lead to this accumulation and the consequences of this accumulation — including obesity, diabetes, metabolic syndrome, and inflammation — can be corrected by changing personal behaviors (51). Thus, restoring energy balance has the potential to completely understand the causes and develop potential interventions for this underappreciated cancer risk factor.

Energy Balance: Weighing in on Cancer

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

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

Although this may seem straightforward, research has shown that energy balance is, in fact, a complex dynamic (see Figure 12). It is not only influenced by calorie consumption and physical activity, but also by numerous other factors including genetics, diet composition, body weight, or body composition, and sleep (see sidebar on Sleep Disturbances and Cancer).

Obesity and Cancer

Obesity increases risk for a growing number of cancers, most prominently the adenocarcinoma subtype of esophageal cancer, and colorectal, endometrial, kidney, pancreatic, and postmenopausal breast cancers (52). It also negatively impacts tumor recurrence, metastasis, and patient survival for several types of cancers (51, 53, 54).

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

Importantly, identifying some of the factors that link obesity and cancer is providing potential targets for treating obesity-related cancers. For example, the knowledge that several of the factors discovered act
Type 2 Diabetes Mellitus and Cancer

Type 2 diabetes mellitus is a complex medical condition caused by a combination of factors, including obesity. Independent of obesity, type 2 diabetes increases an individual’s risk of developing cancer (57, 58). Those with type 2 diabetes are most at risk for developing liver, pancreatic, and endometrial cancers, as well as certain forms of lymphoma (58, 59).

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

Despite the fact that type 2 diabetes affects about 7.5 percent of the U.S. population (61), it is not well established how type 2 diabetes increases cancer risk. Research suggests that it likely influences cancer development in several ways, many of which are similar to the ways in which obesity affects cancer (58, 59). For example, similar to obesity, type 2 diabetes increases levels of insulin and causes persistent inflammation.

Importantly, recent evidence suggests that treatments directed at reducing the hallmark of type 2 diabetes may influence cancer risk. Metformin, which is one of the most commonly used drugs for treating patients with type 2 diabetes, appears to reduce a type 2 diabetic’s risk of developing colon and pancreatic cancers (62, 63). In contrast, sulfonureas, a different class of drugs commonly used to treat type 2 diabetes, may increase risk of cancer development (56). However, further studies are needed to clarify these issues (58). Given what we have learned about the anticancer effects of metformin in patients with type 2 diabetes, numerous clinical studies are underway to assess whether it has the potential to benefit nondiabetic patients with cancer (64).

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

Physical Activity and Cancer

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

In addition, several recent studies indicate that sedentary behavior may increase risk for developing certain cancers and for mortality in cancer survivors independent of physical activity and weight. For example, one study showed that individuals who spent 10 or more years in sedentary work had almost twice the risk of cancers arising in their rectum or in a specific part of their colon compared with individuals who did not spend any time in sedentary work (67). In a second study, patients with colorectal cancer who spent six or more hours a day sitting after their diagnosis had a dramatically increased risk of death from their cancer compared with patients who spent fewer than three hours a day sitting (68). Likewise, a large-scale study also showed that the more time a person spent sitting, the greater their risk of death from any cause, regardless of their level of physical activity (69).

Conversely, research has shown that for patients with certain forms of cancer, including breast, colorectal, and prostate cancers, physical activity improves outcomes by reducing recurrence and increasing survival (8, 70-73). Clear guidelines for physical activity for cancer survivors have been published (8, 65, 66). However, it appears that these have mostly been applied in clinical settings and research interventions, and that they have not yet become general standards of practice in the United States.

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

Looking For Cancer: Who, When, and Where

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

Unfortunately, we have also learned that it is not always easy to identify at-risk patients or those with early-stage disease. However, researchers and clinicians are looking to pair our molecular understanding of cancer development with indicators of cancer risk to create personalized prevention and early-stage intervention programs. For example, some patients may be able to reduce their risk by simply modifying their behaviors. Others might need to increase their participation in screening or early detection programs or even consider taking a preventive medicine or having precautionary surgery (see Tables 6 and 7, pp. 28 and 30, respectively).
How do I Know if I am at High Risk for Developing an Inherited Cancer?

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

Adapted from: http://www.cancer.org/Cancer/CancerCauses/

Classifying Risk

Prevention and Early Detection of Primary Tumors

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

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

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

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

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

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

Table 6: FDA-Approved Medicines for Cancer Risk Reduction or Prevention and Early Detection of Primary Tumors

<table>
<thead>
<tr>
<th>Condition</th>
<th>Generic Name</th>
<th>Trade Name</th>
<th>Formulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast cancer</td>
<td>raloxifene</td>
<td>Evista</td>
<td></td>
</tr>
<tr>
<td>Breast cancer</td>
<td>tamoxifen</td>
<td>Nolvadex</td>
<td></td>
</tr>
<tr>
<td>Cervical, vulvar, vaginal and anal cancers and dysplasia, genital warts</td>
<td>human papillomavirus quadrivalent (types 6, 11, 16, and 18)</td>
<td>Gardasil</td>
<td></td>
</tr>
<tr>
<td>Cervical cancer and cervical dysplasia</td>
<td>human papillomavirus (types 16 and 18)</td>
<td>Cervarix</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Condition</th>
<th>Generic Name</th>
<th>Trade Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Actinic keratosis</td>
<td>ingenol mebutate</td>
<td>Picato</td>
</tr>
<tr>
<td>Actinic keratosis</td>
<td>fluorouracil</td>
<td>Adriocid</td>
</tr>
<tr>
<td>Actinic keratosis</td>
<td>diclofenac sodium</td>
<td>Solaraze</td>
</tr>
<tr>
<td>Actinic keratosis</td>
<td>-aminohexic acid + photodynamic therapy (PDT)</td>
<td>Actinex</td>
</tr>
<tr>
<td>Bladder dysplasia</td>
<td>bacillus calmet pavie/BCG</td>
<td>Valstar</td>
</tr>
<tr>
<td>Bladder dysplasia</td>
<td>valrubicin</td>
<td>Photofoin</td>
</tr>
<tr>
<td>Esophageal dysplasia</td>
<td>perfluroro sodium + photodynamic therapy (PDT)</td>
<td>Photofoin</td>
</tr>
</tbody>
</table>

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

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

Stratifying risk based on age has also worked for colonoscopy, which has contributed significantly to dramatic declines in colorectal cancer incidence and mortality (38). However, only about 59 percent of all Americans aged 50 years and older, the group for whom colorectal cancer screening is currently recommended, get screened (78). Among the more than one-third of Americans who do not follow colorectal cancer screening guidelines is a disproportionately high number of African-Americans (78, 80), a group that shoulders an overly large share of colorectal cancer. The proportion of individuals following colorectal cancer screening guidelines is a disproportionately high number of African-Americans (78, 80), a group that shoulders an overly large share of colorectal cancer.

Table 8: Inherited Cancer Risk

<table>
<thead>
<tr>
<th>Cancer</th>
<th>Syndrome</th>
<th>Associated Gene</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leukemias and lymphomas</td>
<td>Ataxia telangiectasia</td>
<td>ATM</td>
</tr>
<tr>
<td>All cancers</td>
<td>Bloom syndrome</td>
<td>BLM</td>
</tr>
<tr>
<td>Breast, ovarian, pancreatic,</td>
<td>Breast-ovarian cancer syndrome</td>
<td>BRCA1, BRCA2</td>
</tr>
<tr>
<td>and prostate cancers</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Colorectal cancer</td>
<td>Cowden syndrome</td>
<td>PTEN</td>
</tr>
<tr>
<td>Metastasis</td>
<td>Familial adenomatous polyposis</td>
<td>APC</td>
</tr>
<tr>
<td>Retinal cancer</td>
<td>Familial retinoblastoma</td>
<td>RB1</td>
</tr>
<tr>
<td>Colorectal cancer syndrome</td>
<td>Hereditary nonpolyposis colorectal</td>
<td>HNPCC, MSH2,</td>
</tr>
<tr>
<td></td>
<td>cancer/Lynch syndrome</td>
<td>MSH6</td>
</tr>
<tr>
<td>Pancreatic cancer</td>
<td>Hereditary pancreatitis/familial</td>
<td></td>
</tr>
<tr>
<td></td>
<td>pancreatic syndrome</td>
<td></td>
</tr>
<tr>
<td>Leukemias, breast, brain and</td>
<td>Li-Fraumeni</td>
<td>TP53</td>
</tr>
<tr>
<td>soft tissue cancers</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pancreatic cancers, pharyngeal</td>
<td>Multiple endocrine neoplasia I</td>
<td>MEN1</td>
</tr>
<tr>
<td>adenomas, benign skin and fat</td>
<td></td>
<td></td>
</tr>
<tr>
<td>tumors</td>
<td>Thyroid cancer, pheochromocytoma</td>
<td>RET, SF111K</td>
</tr>
<tr>
<td>Pancreatic, liver, lung, breast,</td>
<td>Multiple endocrine neoplasia II</td>
<td>STK11, MEN2B</td>
</tr>
<tr>
<td>ovarian, uterine and testicular</td>
<td></td>
<td></td>
</tr>
<tr>
<td>cancers</td>
<td>Tumors of the spinal cord, cerebellum, retinoblastoma, von Hippel-Lindau syndrome, Wilms, adenoma, kidneys</td>
<td></td>
</tr>
<tr>
<td>Kidney cancer</td>
<td>Wilms’ tumor</td>
<td>WTI</td>
</tr>
<tr>
<td>Skin cancer</td>
<td>Xeroderma pigmentosum</td>
<td>XPD, XPD, XPA</td>
</tr>
</tbody>
</table>

Since 2003, a spectacular successful initiative at eliminating colorectal cancer disparities has been running in Delaware (81). The cancer control program, as it is known, increased colorectal cancer screening among all Delawareans age 50 or older from 57 percent in 2002 to 74 percent in 2009. Moreover, screening rates for African-Americans rose from 48 percent to 74 percent, matching the screening rate among non-Hispanic whites for the same period of time. Perhaps most importantly, disparities in colorectal cancer incidence and mortality rates between non-Hispanic whites and African-Americans were also equalized as a result of the equivalent screening rates between the two groups. The researchers who conducted this study predict that if similar programs could be implemented in all states, racial disparities in colorectal cancer incidence and mortality could be greatly reduced (81). Screening programs have successfully reduced the incidence and mortality for cervical and colorectal cancers because they identify the diseases at an early-stage before they become life threatening, thereby providing opportunities for early intervention. However, not all population-based screening programs have been equally effective. For example, while the prostate-specific antigen (PSA) test is very good at detecting early-stage prostate cancer lesions, it does not distinguish between lesions that will progress to advanced disease and those that will not (88). As a result, many patients undergo unnecessary treatment. Concerns about overdiagnosis and overtreatment have led to the current

Table 7: Surgeries for the Prevention of Cancer

<table>
<thead>
<tr>
<th>Technique*</th>
<th>Prevents</th>
<th>Removes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colpectomy*</td>
<td>Cervical Cancer</td>
<td>Part of large intestine</td>
</tr>
<tr>
<td>Hysterectomy*</td>
<td>Uterine Cancer</td>
<td>Uterus</td>
</tr>
<tr>
<td>Mastectomy</td>
<td>Breast Cancer</td>
<td>Breasts</td>
</tr>
<tr>
<td>Oophorectomy</td>
<td>Ovarian Cancer</td>
<td>Ovaries</td>
</tr>
<tr>
<td>Ovariotomy*</td>
<td>Ovarian Cancer</td>
<td>Ovaries and fallopian tubes</td>
</tr>
<tr>
<td>Salpingo- oophorectomy</td>
<td>Ovarian Cancer</td>
<td>Ovaries and fallopian tubes</td>
</tr>
</tbody>
</table>

“*not commonly performed for the prevention of cancer
Cancer Health Disparities in America

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

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

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

The demographic changes that are anticipated over the next few decades highlight the importance of addressing cancer health disparities in America. By 2050, it is expected that 30 percent of the population will be Hispanic and 15 percent will be African-American (82, 83). Cancer is already the leading cause of death for Hispanics, accounting for approximately 21 percent of deaths overall and 15 percent of deaths of children, and African-Americans are more likely to die from cancer than any other racial group (9). Therefore, the future health of these groups, and all Americans facing cancer, will require the continued generation of new insights into the underlying causes of cancer health disparities, and the implementation of effective interventions for the elimination of these disparities.

One approach to more precisely identify at-risk patients is to use their history. In a study investigating the usefulness of low-dose computed tomography (CT) screening for early detection of lung cancer, current and former heavy smokers aged 55 to 74 years were classified as having the highest risk for developing disease (91, 92). The researchers found that in this population, low-dose CT screening reduced lung cancer mortality by 20 percent because it identified small and early-stage tumors (91, 92). There are an estimated 84 million current and former smokers in the United States; however, the majority of them are unlikely to benefit from screening because they are not heavy smokers (93).

More work is needed to ensure that Americans understand that cancer screening approaches, including low-dose CT screening for early detection of lung cancer, are most clinically effective when targeted at those at highest risk for developing the disease for which they are being screened (94). Targeting those most at risk also has the benefit of decreasing the complications and cost of unnecessary health care interventions for those at low risk of disease. Research to develop new, accurate, and reliable ways to discern an individual’s cancer risk is vital to ensure that the public has confidence in current screening guidelines and any future changes to these guidelines.

Prevention and Detection of Tumor Recurrence

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

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

Cancer Survivorship

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

As a result of advances in cancer research more people are surviving longer and leading fuller lives after their initial cancer diagnosis. In fact, the number of cancer survivors living today in the United States is estimated to have risen to more than 13.7 million, which is approximately 4 percent of our nation’s population (95).

This is a growing population; in fact, it is estimated that the number of cancer survivors living today in the United States is estimated to rise to more than 22 million (96). This expansion can be attributed to numerous factors including earlier cancer detection, which increases the chance for curative treatment; more effective and less toxic treatments, particularly for advanced and metastatic disease, and the aging and growing population.

Also increasing is long-term survivorship. Survivorship rates vary considerably depending on cancer type, patient age at diagnosis, and other characteristics. For example, in the United States in 2012, an estimated 64 percent of survivors were diagnosed with cancer five or more years ago, and 15 percent were diagnosed 20 or more years ago (3). Among children diagnosed with cancer, the chances of long-term survival are even greater: three out of every four American children receiving a cancer diagnosis are alive 10 or more years later (97).

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

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

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

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

It is clear that a person diagnosed with cancer may be faced with critical problems that diminish their quality of life for many years. Thus, a new focus for cancer research is to help the increasing number of cancer survivors achieve a higher quality of life by avoiding or diminishing the potential long-term and late effects of successful treatments. By gaining a better understanding of these issues confronting cancer survivors, the cancer research and advocacy community can continue to play an integral role in meeting the needs of survivors, their loved ones, and future Americans navigating the cancer journey.
production of estrogen have proven very successful at reducing tumor recurrence if taken for five years (96-98) (see Table 6, p. 3). Moreover, recent data from long-term clinical trials indicate that 10 years of therapy with one of these drugs, tamoxifen (Nolvadex), is even more effective at reducing tumor recurrence (99, 100). As all anti-estrogen drugs have serious side effects, our knowledge that these drugs are ineffective for women whose breast cancers are not fueled by estrogen spares these patients from unnecessary and potentially harmful treatments.

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

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

Despite these successes, the use of medical interventions to reduce primary and recurrent tumor risk is not widespread. Therefore, continued research is needed to develop more concrete evidence to identify the most at-risk patients, better screening approaches, and more and better ways to intervene earlier in the progression of cancer.
I am a 17-year ovarian cancer survivor. The knowledge that my survival depended so heavily on chance and good luck fueled my desire to spread awareness about gynecologic cancers, cancer health disparities, and the need for more research funding.

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

To remove fibroid tumors and an ovarian cyst, I had a hysterectomy and bilateral salpingo-oophorectomy. My oncologist discovered the tumorous ovary and contacted a gynecologic oncologist to complete the surgery. In so doing, the probably saved my life and surely increased my chances of recurrence-free survival.

When my gynecologic oncologist called with the pathology report, I told him he had good and bad news. The good news was that it was clear-cell, the most treatable stage. The bad news was that it was clear-cell, the most treatable stage. The bad news was that it was obvious this was not a virus. At my wife’s insistence, not my own, I had colon cancer — later learning it was stage 3.

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

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

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

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

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

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

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

Thou Art, I’ve been spared and I’m forever thankful to God and the wonderful care I received, and continue to receive, in follow-up visits. I have the utmost respect for those in the healing profession — the physicians and scientists who have chosen this path so others may live. They have my heartfelt gratitude.
Stop these T cells from functioning. One way this happens is through the immune system and simultaneously steps on the accelerator to enhance the T cells' killing power.

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

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

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

Decades of Research Now Yielding Results For Patients

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

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

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Releasing the Brakes on the Immune System

Immune cells called T cells (see sidebar on Key Players in the Immune System) are naturally capable of destroying cancer cells; however, many tumors develop sophisticated ways to stop these T cells from functioning. One way this happens is that T cells in the tumor microenvironment display on their surface multiple other types of immune responses. For example, they release factors, or cytokines, that direct the function of other immune cells. CD8+ T cells that produce the cytokine interferon-γ are sometimes called T helper 1 cells, or Th1 cells. They release factors that kill their target.

When they become activated, Th1 cells release factors that kill their target. They do not kill their target, rather they orchestrate the “first responders” of the immune system. When called into action, they release factors that kill their target. T cells, or T lymphocytes, are divided into two main types: those that have the protein CD4 on their surface (CD4+ T cells) and those that have the protein CD8 on their surface (CD8+ T cells). CD4+ and CD8+ T cells both “identify” their target through a group of proteins on their surface called T-cell receptors.

CD4+ T cells are sometimes called cytotoxic T cells or killer T cells. When they are called into action, they attack and destroy their target. CD8+ T cells respond differently to CD4+ T cells when called into action. They do not kill their target, rather they orchestrate multiple other types of immune responses. For example, they release factors, or cytokines, that direct the function of other immune cells. CD8+ T cells that produce the cytokine interferon-γ are sometimes called T helper 1 cells, or Th1 cells.

A distinct subset of CD8+ T cells keeps other immune cells in check, preventing them from attacking our own normal cells and from over responding to pathogens. These cells are called regulatory T cells, or Treg cells.

Some cancers actively recruit Treg cells to help shut down the anticancer immune response. B cells, or B lymphocytes, respond to pathogens and cancer by releasing factors called antibodies. Each B cell makes a single antibody. Monoclonal antibodies, one of the most important classes of anti-cancer therapy, are derived from the progeny of a single B cell selected to produce one antibody with high specificity for the therapeutic target of interest.

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

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

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

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

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

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

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

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

The development of ipilimumab resulted directly from a series of milestone discoveries by scientists in the field of immunology. What is most exciting about ipilimumab, is that some patients who responded are still alive three, four, five years after receiving their treatment. This is something that has rarely happened before for patients with metastatic melanoma, and it indicates that even after the treatment was stopped, these patients’ immune systems are still keeping their tumors in check.

In 2012 and 2013, the results of early-stage clinical trials testing immunotherapies that disable a second immune-system brake, called PD1, showed even more dramatic results. These studies reported frequent clinical responses not only for patients with metastatic melanoma, but also for those with kidney or lung cancer.

Although these PD1-targeted treatments are not approved by the FDA currently, patients’ responses seem to be long-lived, and everyone involved in the development of these drugs expects that they will soon become widely available.

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

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

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

There are barriers to this becoming a reality, but they are not scientific. They are regulatory and financial. To use a military analogy, we have the weapons but not the funds to test or use them effectively.
agents can exert anticancer effects on the surface of a cell. These effects are mediated by a defined molecule on the cell surface, which is a protein that attaches to a defined molecule on the surface of the cell.

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.

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

The story of immune checkpoint proteins began in 1987, when researchers discovered a gene that they called CTLA4. It then took nearly eight years before the function of CTLA4 was uncovered, and another 16 years before the knowledge was translated into ipilimumab. There are now several other drugs in development against another immune checkpoint protein, called PD1, as well as therapies that target another immune checkpoint protein, called PD-L1.

In some patients, ipilimumab’s effects on the immune system generate durable responses. In fact, about one in every five patients treated with only four doses of ipilimumab are still gaining benefit from it more than four years after completing therapy (105, 107). Ongoing clinical studies are investigating whether additional doses of ipilimumab can offer further benefit to patients like Andrew Messinger. Encouraging early results suggest that ipilimumab might also be effective against advanced lung cancer (106) and advanced prostate cancer (109), but these need verification in larger clinical trials.

The amazing success of ipilimumab has motivated researchers to develop similar therapies that target another immune checkpoint protein, called PD1, as well as therapies that target the protein to which PD1 attaches, PDL1.

In November 2013, ipilimumab (Yervoy) was approved by the U.S. Food and Drug Administration (FDA) for the treatment of metastatic melanoma, and the FDA approved it for this use in March 2011. ipilimumab (Yervoy) is an immunotherapy that works by counteracting brakes on the immune system called immune checkpoint proteins. It was the first drug of its kind to be approved by the FDA. Almost 25 years of basic, translational, and clinical research underpinned the development of ipilimumab.

The designation is granted after all clinical trials are completed, when the drug’s safety and efficacy can be reliably evaluated. Radium Ra 223 dichloride (Xofigo) was granted priority review status in March 2011.

The FDA may grant fast track status to a drug candidate that is intended for serious and life-threatening conditions. This designation is intended to facilitate the development and expedite the review of drugs that fill an unmet medical need. This designation can be granted to a drug candidate at any stage of development.

As a result of these encouraging data, the FDA granted nivolumab fast track designation for these cancers. The FDA approved nivolumab (Opdivo) for the treatment of advanced melanoma and ipilimumab for the treatment of chronic lymphocytic leukemia.

Breakthrough Therapy

Since 2012, experimental therapies that show substantial improvement over available treatment in early clinical studies are eligible for the breakthrough therapy designation. A drug that receives this designation is eligible for all of the features of fast track designation (see below) and additional guidance from the FDA throughout the drug development process. As of Aug. 1, 2013, six anticancer drugs had received this designation, including two immunotherapeutic, ipilimumab for the treatment of advanced melanoma and obinutuzumab for the treatment of chronic lymphocytic leukemia.

Fast Track

Fast track is designed to facilitate the development of drugs that fill an unmet medical need. This designation can be granted solely on the basis of preclinical data, or data from nonhuman studies. Fast track applications may be evaluated through a “rolling” or continual review procedure that allows sponsors to submit to the FDA parts of the application as they are completed, rather than waiting until every section is finished. Ipilimumab (Yervoy), a treatment for metastatic melanoma, was approved through fast track in March 2011.

Accelerated Approval

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

Priority Review

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

Nivolumab, pembrolizumab, and durvalumab are currently undergoing clinical trials to further evaluate their potential as immunotherapies.

Table 9: PD-1 or PD-L1 Targeted Therapeutics Under Development

<table>
<thead>
<tr>
<th>Agent</th>
<th>Targets</th>
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<tbody>
<tr>
<td>Ipilimumab</td>
<td>PD-1</td>
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<tr>
<td>Nivolumab</td>
<td>PD-1</td>
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<tr>
<td>Pembrolizum</td>
<td>PD-L1</td>
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<tr>
<td>Durvalumab</td>
<td>PD-L2</td>
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<tr>
<td><em>MPDL244</em></td>
<td>PD-1</td>
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*antibody-like protein

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

It was 2005 when I first noticed a mark on my chest and went to see my dermatologist. He thought it was a blood blister, but we were both very surprised when the biopsy revealed that it was melanoma. My dermatologist referred me to Memorial Sloan-Kettering Cancer Center in New York, where I had the lesion surgically removed. I also had a sentinel lymph node biopsy. Unfortunately this showed the cancer had spread to my lymph nodes and I had to have a second surgery to have lymph nodes removed. Although scans showed no sign of metastases in my body, the fact that the cancer was in my lymph nodes meant that my diagnosis was advanced disease.

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

Fortunately, I was able to get the initial interferon treatments locally, in suburban New Jersey. That helped a lot. After that, I continued to see multiple doctors to get their opinions, I decided that it was right for me. Psychologically, I just felt I needed to be treated.

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

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

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

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

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

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

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

Special Feature on Immunotherapy

has also designated lambrolizumab, a second therapeutic antibody that targets PD-1, as a breakthrough therapy for advanced melanoma, after it was reported to benefit patients (14) (see sidebar on FDA Designations, p. 41).

Despite the dramatic responses seen in some patients treated with ipilimumab, or an agent targeting PD-1 or PD-L1, these individuals are a small fraction of the total number of people affected by cancer. Perhaps the greatest promise of immunotherapy lies in combining immunotherapies that target different immune checkpoint proteins or immunotherapies that operate differently, as well as combining immunotherapies with other types of anticancer treatments.

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

Boosting the Killing Power of the Immune System

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

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

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

Another cancer vaccine clinical trial that has recently reported very encouraging early results is assessing the effectiveness of a combination of two vaccines, GVAX Pancras and CRS-207, as a treatment for advanced pancreatic cancer (121). The two vaccines work together to boost patients’ immune systems in different ways. GVAX Pancras comprises pancreatic cancer cells that release GM-CSF, which generally enhances immune system function. CRS-207 is a non-toxic bacterial vaccine engineered to carry a protein that will boost the killing power of patients’ immune cells. Experiments in mice originally showed that...
My daughter Maddie was diagnosed with acute lymphoblastic leukemia (ALL) when she was just three years old. She has been treated with all kinds of caustic chemotherapies and head-to-toe radiation therapy. But in January 2013, she received a therapy unlike any other she has been treated with: a T cell therapy that is helping her own body fight the leukemia without serious side effects.

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

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

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

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

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Within days Maddie started relapse therapy. This involved six chemotherapy in October 2010, but life without treatment did not last long. We found out in February 2011, that she had relapsed. When we had known this 10 days ago, our Christmas would have been much happier.

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

Maddie’s experience has made me an advocate for research into new and better targets for antibodies, as well as work on modifying the cancer cells (see Appendix Table 1). Many of the therapeutic antibodies that have been approved by the FDA for the treatment of certain cancers (see Appendix Table 1, p. 81), and many of those in clinical trials, do just that. They operate, at least in part, by attaching to cancer cells expressing their target, flagging them for destruction by immune cells. Research into new and better targets for antibodies, as well as work on modifying the antibody to help the immune system find it more easily, are creating exciting new experimental immunotherapies.

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

Cancer Research At Work Against Other Diseases

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

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

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

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

Recent advances in targeted therapies for patients with metastatic melanoma, brain cancer, and other tumors have led to the development of agents that block the activity of specific proteins involved in tumor progression. As a result, many patients with advanced cancer are no longer treated with toxic chemotherapy drugs that cause nausea and hair loss.

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

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

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

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

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

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

Since February 2004, the FDA has approved nine drugs that work in similar ways to impede the growth of new blood and lymphatic vessel networks that enable cancer cells to thrive (see Table 3, p. 18). These drugs mainly function by stopping members of a family of growth-promoting proteins called VEGFs from activating the molecules they attach to, VEGF receptors, which are mostly found on blood and lymphatic vessel walls.

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

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

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

In February 2013, the FDA approved Pomalidomide (Pomalyst) for the treatment of multiple myeloma. Pomalidomide is a member of a family of drugs called immunomodulatory drugs. These drugs fight multiple myeloma by modulating aspects of the immune system and by reducing the production of VEGFs, which leads to disruption of new blood and lymphatic vessel networks (141). Importantly, several cancers. Leveraging our current knowledge of conventional chemotherapies and of the precision targeting of anticancer antibodies to develop new antibody-drug conjugates not only improves patient care by reducing side effects, but it also increases the return on prior investments in cancer research.
Drug Resistance

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

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

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

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

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

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

Lessons Learned From CML

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

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

Three FDA decisions in the last four months of 2012 should help address this serious clinical issue and has increased the number of treatment options for patients with imatinib-resistant CML. The first was the September 2012 FDA approval of ponatinib (Iclusig). Like imatinib, dasatinib, and nilotinib, ponatinib blocks the activity of BCR-ABL, but fails to block the T315I BCR-ABL mutant. Its use as a treatment for CML was approved by the FDA after it was shown to have anti-leukemic activity in patients with CML resistant to one or more of imatinib, dasatinib, and nilotinib (144). The second was the October 2012 FDA approval of omacetaxine mepesuccinate (Symobio). Understanding how omacetaxine mepesuccinate works is an area of active investigation; currently, it seems that omacetaxine mepesuccinate benefits patients with multiple myeloma that has progressed after treatment with earlier generation immunomodulatory drugs (142).
I sought a second opinion from Dr. Druker at the Knight Cancer Institute. I was told my best option was to begin taking dasatinib (Sprycel). Thirty days later, my first blood test showed positive signs. At that point, I was in complete shock. I am an avid soccer player. In the fall of 2008, I started feeling extremely tired during games and having to sub out a lot. I was also experiencing night sweats. My wife talked me into going to see my doctor. He sent me for a bone marrow biopsy. The results showed that I had CML.

I was sent for a bone marrow biopsy. The results showed that I had CML. My hopes and dreams were taken from me in December 2008, when I was diagnosed with chronic myelogenous leukemia (CML) (146). Most dramatically, it was effective for nearly all patients with CML harboring the T315I BCR-ABL mutant (145). In 2011, the FDA revolutionized the treatment of metastatic melanoma, the most aggressive form of skin cancer, when it approved vemurafenib (Zelboraf). This drug blocks an abnormal form of the signaling protein BRAF, called BRAF V600E, which fuels about 45 percent of melanomas (147). Thus, the FDA approved the use of vemurafenib only for patients who have metastatic melanoma shown to be driven by BRAF V600E as identified using a special test, a companion diagnostic, called the cobas 4800 BRAF V600 Mutation Test (see sidebar on Companion Diagnostics).

Unfortunately, Dr. Druker was right. After taking dasatinib for three months, analysis of my bone marrow showed my leukemia had not responded to treatment. A second mutation analysis provided the explanation: my leukemia cells carried the T315I mutation that made them resistant to imatinib, dasatinib, and all other targeted therapies approved for CML at the time. A bone marrow transplant seemed to be my only option, and I began preparing for it. However, I wanted to avoid it if possibly could. I couldn’t foolishly be going through a physically extreme treatment that would involve my being unable to help my children for 100 days.

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

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

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

I don’t directly block BCR-ABL activity but rather reduces levels of mutant, protein. Perhaps as a result of its unique mode of action, early clinical studies indicate that omacetaxine mesylate has clinical benefit in patients with CML harboring the T315I BCR-ABL mutant (145). The third decision is the December 2012 FDA approval of ponatinib (Iclusig), a drug that is transforming the lives of patients like Hans Loland, who has CML harboring the T315I BCR-ABL mutant. The development of ponatinib culminated in a clinical trial that showed that ponatinib benefited patients with CML resistant to multiple other BCR-ABL–blocking drugs (146). Most dramatically, it was effective for nearly all patients with CML harboring the T315I BCR-ABL mutant. Although it is too soon to tell how long ponatinib will control disease, early signs are very promising.

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

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

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

Employing just two or three companion diagnostics, the FDA approved the use of vemurafenib only for patients who have metastatic melanoma shown to be driven by BRAF V600E as identified using a special test, a companion diagnostic, called the cobas 4800 BRAF V600 Mutation Test (see sidebar on Companion Diagnostics).
patients with metastatic non-small cell lung carcinoma driven by either of the mutations detected by the diagnostic — EGFR exon 19 deletions or an EGFR exon 21 L858R substitution. Prior to the approval of the companion diagnostic, oncologists could only use erlotinib to treat patients with metastatic non-small cell lung carcinoma after they had received at least one other therapy. Thus, the companion diagnostic is helping a substantial number of patients with non-small cell lung carcinoma save time in their quest to find the best drug to treat their cancer.

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

Closing RANK on a Rare Bone Tumor

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

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

Technology Advances for Patient Benefit

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

Nanotechnology: Tiny Technologies Make a Big Impact

Nanotechnology refers to the manufacturing of objects with dimensions one million times smaller than a millimeter (the smallest width of a human hair is just fifty times smaller than a millimeter). Nanomedicine is the application of nanotechnology to the research and practice of medicine. Nanodrugs comprise an anticancer agent and a nanosized carrier that is designed in such a way that it selectively delivers the drug to the cancer and protects the drug from being destroyed by the body’s defenses during transport. As a result, nanodrugs allow the delivery of higher levels of anticancer agents to cancer cells than traditional systemic delivery methods, increasing effectiveness while reducing toxic side effects.

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

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

Mapping Cancer’s Escape Route

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

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

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

Later that year, I started experiencing pain in my lower left abdomen. I underwent all sorts of tests, most of them failed to identify a cause of my pain. But I did not give up hope completely, and when my daughter-in-law heard about a clinical trial for pancreatic cancer that was having amazing results, I knew I wanted to give it a try. Within a month of receiving the trial drug Abraxane (a nanoparticle form of paclitaxel) I started feeling better.

During that time, I have been treated with nanoparticle paclitaxel on and off, mostly at the Mayo Clinic, but recently at Scottsdale Healthcare for patients with metastatic pancreatic cancer. She had been told that the drug being tested, nanoparticle paclitaxel, was having dramatic effects and suggested this as a possible treatment for my cancer. As my endoscopic biopsy had been performed at the Mayo Clinic, I began my journey with nanoparticle paclitaxel in combination with a chemotherapy called gemcitabine (Gemzar), at the Mayo Clinic.

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

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

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

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

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

Clear Images with Lower Radiation Doses

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

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

One approach to limit radiation exposure from CT scans is to develop new machines that use lower doses of ionizing radiation. In September 2012, the FDA approved one such machine, the Aquilion One Vision CT scanner that provides high-quality images using lower radiation doses than previous generation CT scanners (163). As technology continues to advance, progress in this area is expected to continue. When combined with educational programs to reduce the number of these procedures and to reduce radiation doses to only what is medically necessary, further decreases in cancer risk should be seen.
abnormal proteins and/or the disrupted cell behaviors. These molecularly targeted drugs are providing patients with some forms of cancer with less toxic and more effective treatment options, thereby realizing the promise of precision medicine.

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

One message that is emerging from analysis of the genomic data is that there are about 140 genes that, when altered, can promote, or drive, the development of cancer (166). More significantly, these driver genes produce proteins that participate in perhaps only a dozen molecular networks (Figure 16, p. 60). The fact that the same driver genes and networks are disturbed in different cancers is changing the way that researchers view and, more importantly, how clinicians treat cancer. Increasingly, cancer is viewed as a group of genetic diseases, defined not only by where they originate — in the brain, breast, liver, lung, etc. — but also by the genetic alterations that are driving their formation.

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

Figure 16: The Long and Winding Road to Genomic Medicine.  

Large-Scale Genomic Initiatives

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

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

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

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

St. Jude Children’s Research Hospital, in Memphis, Tenn., and Washington University, in St. Louis, Mo., joined forces in 2010 to sequence the genomes of both normal and cancer cells from more than 1,000 children with cancer. This PGP (pediatriccancergenomeproject.org) is the largest investment to date aimed at understanding the genetic origins of childhood cancers.

The data generated by these initiatives are already reshaping our definition of cancer. We now understand that many cancers are caused by genetic changes, or mutations, that lead to altered proteins and disruption of normal cell behaviors, and use this knowledge to develop anticancer drugs that target these proteins. But it was almost 40 years before the chemical structure of deoxyribonucleic acid (DNA) was published that Theodore Boveri first suggested that genomic abnormalities might cause cancer. Highlighted here are just some of the research milestones that have led to current understanding of the genome’s relevance to cancer development. As with all research, the more knowledge that is obtained, the more rapidly new discoveries can be made. In the area of genomic medicine, technology has been a tremendous catalyst for speeding these discoveries. The DNA strand symbol indicates genetic and/or genomic discoveries about the nature of DNA and/or the genome; the cell symbol indicates genetic and/or genomic discoveries about the nature of cancer; the DNA bolt symbol indicates technological breakthroughs; and the stethoscope symbol indicates research advances with treatment or diagnostic implications.
Figure 17: Many Mutations, a Single Outcome: Growth Advantage. The message that is emerging from analyses of genomic data is that there are about 140 genes that, when altered, can drive the development of cancer. More significantly, these driver genes produce proteins that participate in perhaps only a dozen molecular networks (166), each of which can give a cancer cell a competitive growth advantage. These networks and cellular activities are depicted, grouped by the way they impact a cancer cell’s growth advantage. However, each network also affects other cellular functions.

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

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

Recently, two independent large-scale genomic studies provided insight that could benefit some patients with breast cancer harboring HER2 gene mutations but not amplifications. HER2 gene that causes the HER2 protein to be overactive in the same way that HER2 gene amplification does, suggesting that they might be sensitive to HER2-targeted therapies. Thus, a clinical trial has been launched to evaluate whether the investigational HER2-targeted therapy neratinib is a good treatment option for patients with metastatic breast cancer harboring HER2 gene mutations but not amplifications.

I am in my 12th year of treatment for metastatic breast cancer. Although I have been in treatment constantly since my diagnosis, I have lived, and continue to live, a full and productive life. In 2012, I had my tumor genetically profiled. This empowered me. It enables me to search for clinical trials of new drugs that might keep me alive with minimal toxicity so that I can continue enjoying life. My journey with cancer began in 2001 when I went to my general practitioner because I was tired, so tired I was having trouble completing simple tasks. He told me he felt an enlarged liver and sent me for a CT scan. The scan revealed tumors in my liver. At the time they thought it was liver cancer, but biopsies showed that it was not. It was breast cancer. I was metastatic from day one. My first thought was: How long do I have to live? Is there any chance of survival? I felt I had to say goodbye to my future.

But the reality is that I joined a vibrant group of people living with metastatic breast cancer. You might not recognize us, we may look just like you, we are not cancer survivors; we are surviving with cancer, constantly receiving treatment. In essence, we live two parallel lives. For me, for the first two years after diagnosis, one life was a series of chemotherapy and radiation treatments that reduced levels of tumors in my body. The other was a full-time job, a busy home life, and family obligations.

At the end of the two years, my tumor markers had dropped to levels found in healthy women, and CT scans showed no evidence of disease. I was placed on hormone therapy, exemestane (Aromasin), and for the next five years I lived an almost normal life. At that time, a tumor again appeared in my liver. After radiofrequency ablation of the tumor and six months taking everolimus (Afinitor) might be effective against my cancer. Unfortunately, the results of the genetic analysis indicated that everolimus (Afinitor) might be effective against my cancer. Unfortunately, that was not the case.

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

My research oncologist explained that currently, genetic analysis is not all-encompassing because knowledge today has its limits. He also said that our knowledge is rapidly expanding and that in time genetic analysis will play a more comprehensive picture of tumors. Although genetic analysis failed to identify a drug that benefited me, the power that it gave me was priceless, and I would recommend it to anyone in my position. I am currently receiving an investigational drug through a phase Ib clinical trial. It is one of very few options left to me. The reality is that I am at the end of approved treatments. I rely on investigational drugs and the researchers who are identifying new ones.

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

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

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

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

“Umbrella” trials are another approach that researchers are exploring as a possible way to improve the efficiency of clinical trials. Whereas in basket studies researchers test the effect of a single drug, on a single mutation in a variety of cancer types, umbrella studies are designed to test the impact of different drugs on different mutations in a single type of cancer. In the BATTLE umbrella trial, for example, researchers recruited non-small-cell lung cancer patients, genetically profiled their tumors to determine which mutations they had, and then assigned them to receive a particular drug expected to target their mutations. Basket and umbrella studies represent novel approaches to testing targeted therapies. Both types of studies have the potential to accelerate the drug development process so that the right therapies can quickly be delivered to the right patients.

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

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

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

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

On the Horizons

In this section you will learn:

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

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

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

The Near Horizon

As discussed throughout this report, cancer cells are rife with genetic alterations that give them a competitive growth advantage when compared to noncancerous cells. Cancer research has provided us with the ability to identify these alterations and to develop novel and effective medicines that target cancer cells with some of them. Due to large part in the presence of many different alterations within a patient’s cancer, however, cancers can adapt and fuel their growth through an alteration other than the one blocked by a given medicine. This leads to continued or worsened disease.

Near-term breakthroughs against cancer are likely to come from simultaneously blocking the alterations that drive the primary and adaptive growth advantages, forcing the cancer to stop growing and ultimately die. This approach has been successfully used for decades using combinations of a variety of cytotoxic, or nontargeted, chemotherapies, but these have lacked the precision of our current medicines and often are highly toxic. Within a few years we are likely to see many more clinical trials evaluating molecularly targeted therapies in rational combinations determined by our enhanced understanding of cancer biology. In fact, some early trials testing rational combinations of molecularly targeted therapies are underway. For example, the combination of dabrafenib and trametinib, which block different components of the same cancer-driving signaling network, is already showing promise as a treatment for some patients with metastatic melanoma (150) (see Two Drugs: One Cancer-driving Pathway, p. 53). Likewise, a combination of two immunotherapies that target different immune checkpoint proteins, ipilimumab and nivolumab, are showing early benefit for patients with advanced melanoma (115) (see Releasing the Brakes on the Immune System, p. 38).
This approach, however, requires that we understand enough about the underlying biology of cancer to be able to accurately predict the alternative growth advantages most likely to be used by the cancer. The knowledge required to do so will come from a variety of sources including whole-genome sequencing, patient-derived xenograft testing (see sidebar on Patient-derived Xenografts), and predictive mathematical modeling of cancer behavior using systems biology and evolutionary theory.

Even armed with this deeper understanding of cancer biology, much work needs to be done to determine the order, duration, and dosing of the combination of anticancer agents being used. Here again, mathematical modeling and systems biology approaches will be critical to narrowing the nearly infinite permutations into a manageable subset that can be tested in clinical trials. Perhaps one of the most intriguing areas of combination therapy will be adding the new immunotherapies to radiotherapies, chemotherapies, and molecularly targeted therapies to enhance clearing of the tumor by the immune system (see Special Feature on Immunotherapy, p. 38).

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

The Distant Horizon

Of the nearly 3 billion bases in the human genome, only about 1.5 percent code for the various proteins a cell uses to function. Just more than a decade ago, researchers made the important discovery that some of the remainder of the genome codes for molecules called noncoding RNAs, which naturally regulate gene usage and therefore the production of proteins. Since that discovery, small, synthetic noncoding RNAs and DNAs have become vital tools in research laboratories worldwide. Researchers are also exploring the possibility that their ability to dampen gene usage and protein production can be exploited for patient benefit. Unfortunately, the use of synthetic noncoding nucleotides (DNA or RNA) in this way has been hampered by our inability to effectively deliver them to a patient’s cancer.

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

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

In this section you will learn:

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

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

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

Advancing Regulatory Science and Policy

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

For example, it will be necessary to develop improved approaches to identifying, qualifying, and validating biomarkers (see Figure 18 p. 66), particularly since their use is becoming increasingly important for developing effective diagnostic tools and therapies and making treatment decisions. Likewise, advances in clinical trial design are needed if we are to test drugs more rapidly and efficiently. This is particularly important for the evaluation of molecularly targeted drugs that attack cancers by honing in directly on the genetic and molecular abnormalities that drive them (see sidebar on Moleculally Informed Clinical Trials, p. 62). To advance regulatory
science and policy, the FDA must have the resources to recruit and retain highly qualified staff, as well as develop new tools and techniques. They must also have the means to fully engage with the broader scientific community in discussion about areas of scientific progress so that the work of this important agency will benefit from the latest advances in the field. Likewise, these interactions also benefit the broader scientific community by providing it with a better understanding of regulatory policies, facilitating the translation of discoveries into new and improved therapies.

Engaging Patients in Clinical Research

Clinical studies, particularly clinical trials, are a key component of cancer research (see sidebar on The Virtuous Cycle of Biomedical Research, p. 9) because they enable researchers to demonstrate that therapies showing promise in the laboratory are safe and effective for use in people. Typically, researchers conduct randomized clinical trials wherein experimental interventions are tested against the current standard of cancer care in patients and, in some cases, healthy volunteers. Although patient participation in these studies is critical, fewer than 5 percent of adult cancer patients participate in a clinical trial (173). An even smaller fraction of patients from specific subgroups, like the elderly, women, racial and ethnic minorities, and people living in rural areas, participate in clinical trials, which leads to a lack of understanding of whether a drug is safe and effective in these populations. Low participation can slow the progress of clinical trials and delay the development of new therapies.

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

Integrating Research and Patient Care

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

Improving Biospecimen Repositories

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

Cultivating a Highly Skilled and Diverse Cancer Research Workforce

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

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

In addition to providing the resources to recruit and retain talent to science, we must equip our workforce with the knowledge and skills to be able to conduct 21st century cancer research. This means continuing to provide world-
class training in basic, translational, and clinical research; ensuring trainees have access to cutting-edge tools and techniques; ensuring all researchers can participate in the latest scientific meetings and conferences; and cultivating the skills they will need to succeed in the interdisciplinary research teams that have become commonplace. Researchers across the entire biomedical research enterprise must also have access to professional development resources and support, including access to effective mentors, training in laboratory management, opportunities to hone their grant and manuscript writing skills, and exposure to the breadth of career opportunities in the relevant sciences.

In this section you will learn:
• why Congress must make funding cancer research and biomedical science a national priority; and
• the future of the biomedical research enterprise is threatened by sequestration and a declining research budget.

Funding Cancer Research and Biomedical Science Drives Progress

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

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

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

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

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

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

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

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

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

Funding for all NIH research programs generates scientific discoveries that can benefit research spectrum — reducing the number of promising grant proposals that can be funded, potentially leaving the next cancer therapy or cure on the cutting room floor. Furthermore, these cuts impact existing cancer research projects and cancer centers, where critical “bench-to-bedside” research and care take place.

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

In the late 1980s, following a period of stagnant budgets for medical research, Congress and the administration made a bipartisan, forward-thinking decision to double the NIH budget over a five-year period. Unfortunately, in the 10 years since the doubling ended in 2003, the NIH budget has been steadily shrinking because the amount of funding provided to the agency each year has been less than what is needed to keep pace with biomedical inflation (see Figure 19). This has effectively decreased the NIH’s ability to fund lifesaving research.

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

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

Figure 19: Effective Losses with a Significant Impact. The biomedical research and development index (BRDPI) reflects the rising cost of personnel, supplies, and equipment needed to conduct biomedical research. In the past decade, the National Institutes of Health (NIH) budget has not kept pace with the BRDPI. As a result, the NIH has effectively lost approximately 25% of its ability to fund lifesaving research (178).

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

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

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

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

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

Life Under Sequestration

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

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

Consider the numbers: NIH

<table>
<thead>
<tr>
<th>FY 2012 funding level</th>
<th>$30.6 billion</th>
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<tbody>
<tr>
<td>2013 across-the-board cut (5.1 percent)</td>
<td>-$1.6 billion</td>
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<tr>
<td>Current FY 2013 level</td>
<td>$29 billion</td>
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<tr>
<td>Reductions in competing NIH grants</td>
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<tr>
<td>Reduction in total funded grants</td>
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<tr>
<td>Potential U.S. Job loss</td>
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<tr>
<td>Expected Reduction in economic activity</td>
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For information on the current status of NIH funding, go to http://cancerprogressreport.org/Pages/FederalFunding.aspx

American Association for Cancer Research
The AACR Call to Action

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

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

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

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

References

17. Results from the 2010 National Survey on Drug Use and Health: summary of national findings. Rockville, MD: Substance Abuse and Mental Health Services Administration; 2011.
References

Acute lymphocytic leukemia (ALL) — An aggressive (fast-growing) type of leukemia (blood cancer) in which too many abnormal white blood cells (WBCs) are in the blood and bone marrow. Also called acute lymphoblastic leukemia.

B cell — A type of immune cell that makes proteins, called antibodies, which bind to microorganisms and other foreign substances, and help fight infections. A B cell is a type of white blood cell. Also called 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 lymphoblastic leukemia (ALL). The Philadelphia chromosome or Philadelphia translocation is a specific chromosomal change (inversion 9;22) in the BCR gene on chromosome 22 that forms the BCR-ABL fusion gene, which makes the BCR-ABL protein.

Biomedical Research Infusion — Biomedical research is calculated using the Consumer Price Index (CPI) in the United States. It is the least expensive of the three methods, which includes how much the NIH budget must change to maintain purchasing power. Over the years, biomedical research inflation has been double the economy-wide inflation rate on average.

Biopsies — A type of tissue sample for doctors to perform medical tests. Needle biopsy is usually the first step to see if the cancer is malignant or benign. If so, more advanced biopsy techniques may be done (open incision, incisional biopsy, or needle core biopsy).

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.

BRAC往往发由BRAC基因产生的。它位于染色体2号的BRAC位点，形成BCR基因，导致免疫性血癌，特别是在骨髓中。BCR是BCR基因产物，其作用是调节细胞的生长和存活。随着年龄的增长，BCR的作用会逐渐减弱。

BRCA1 or BRCA2 gene has a higher risk of getting breast, ovarian, prostate, and skin cancer in patients who are not carriers of a family history of breast cancer. If a woman has a BRCA1 or BRCA2 gene mutation, there is a 60% to 70% chance that she will develop breast cancer by the age of 50 and an 80% to 85% chance that she will develop breast cancer by the age of 70. Men who have a BRCA1 or BRCA2 gene mutation have a 5% to 8% chance of developing breast cancer, prostate cancer, ovarian cancer, or skin cancer.

Breast cancer occurs in both men and women, although male breast cancer is rare. Although many patients who are affected with BRCA-related cancer may not have symptoms, breast cancer may be more likely to develop in older women, or in those who are at a higher risk of developing breast cancer. BRCA-related cancers may also have a higher risk of recurrence in older types of non-Mullerian types of tumors.

BRCA is a human gene that is located on the chromosome 17. It is a tumor suppressor gene, which means that it is responsible for maintaining the balance of cell growth and cell death. BRCA gene mutations are known to increase the risk of developing breast, ovarian, prostate, and skin cancer.

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

Chemokine — A small protein that is released by immune cells and that attracts other immune cells to the site of infection. Chemokines are produced by many different types of cells, including immune cells, cancer cells, and by the stroma.

Chemotherapy — The use of drugs that can kill or slow the growth of cancer cells. These drugs work by destroying abnormal cells, including cancer cells. Chemotherapy is usually given as a treatment for cancer, but it can also be used as a prophylactic (preventive) treatment for cancer.

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Cytotoxic T lymphocyte antigen-4 (CTLA-4) — A protein on the surface of activated cytotoxic T lymphocytes that inhibits the ability of these cells to kill cancer cells. CTLA-4 binds to a molecule called CD80 on the surface of antigen-presenting cells, which prevents the activation of CD8 T lymphocytes.

Cytostatic chemotherapy — Antitumor drugs that kill cells, especially cancer cells.

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Cytokine — A type of immune cell that makes proteins, called cytokines, which bind to receptors on other cells and help regulate the immune response. Cytokines are produced by many different types of cells, including immune cells, cancer cells, and by the stroma.

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Cystic fibrosis (CF) — A genetic disorder that affects the lungs, pancreas, and other organs. CF is caused by mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene, which is located on the long arm of chromosome 7. CFTR is a protein that helps regulate the flow of salt and water in the cells. CFTR deficiency leads to the accumulation of thick, sticky mucus in the airways, which can cause breathing problems, coughing, and recurrent lung infections.

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Pancrectic cancer – A group of cancers that start in the 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 main concern of these cancers are called acinaradenoma. Pancreatic cancers that arise in the cells of the pancreas that help control blood sugar levels are called pancreatic neuroendocrine tumors.

Polycystic kidney disease (PKD) – A family of proteins that work inside cells to send signals that direct normal cellular function, including cell growth, proliferation, and division. The gene that encodes one component of one PKD is mutated, resulting in an inappropriate activity in many proteins in many types of cells, including the kidney cells.

Poly A – An oligonucleotide that promotes an expression of a gene.

Prophylactic splenectomy – A surgery that is performed to prevent complications caused by the spleen. It is performed on individuals who are at risk of developing life-threatening infections.

Prostate cancer – A form of cancer that starts in the prostate gland. The prostate gland is located below the bladder and in front of the rectum. It is the most frequently diagnosed cancer and the second most common cause of death from cancer in men. It affects men of all ages, but it is most common in men aged 45 and older.

Prostate-specific antigen (PSA) – A protein secreted by the prostate gland into the urine. It is used as a test to check for prostate cancer. A higher level of PSA is associated with an increased risk of prostate cancer.

Proteins – A macromolecule made up of amino acids that is needed for the body's function to work properly.

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

Radiotherapy – The use of high-energy radiation to destroy cancer cells, tumors, and other cells or tissue. Radiotherapy may be used to treat cancer or to relieve symptoms of cancer.

Receptors – A protein that is found on the cell surface. It is responsible for recognizing and responding to specific ligands. Receptors are most commonly activated by ligands from outside the cell, in a lock-and-key manner, producing a specific effect on the cell.

Signaling pathway – A series of proteins that are activated one after the other in a specific sequence. A signaling pathway is a series of reactions that transmit a signal from the cell surface to the nucleus of the cell.

Signal pathway/signaling network – A group of molecules that work together to control one or more functions, such as cell proliferation or cell death. After the first molecule in a signaling 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 arrest cell cycle.

Standard of care – The治疗方法 used to treat a particular disease or disease. It is recommended by experts and is the foundation of medical practice.