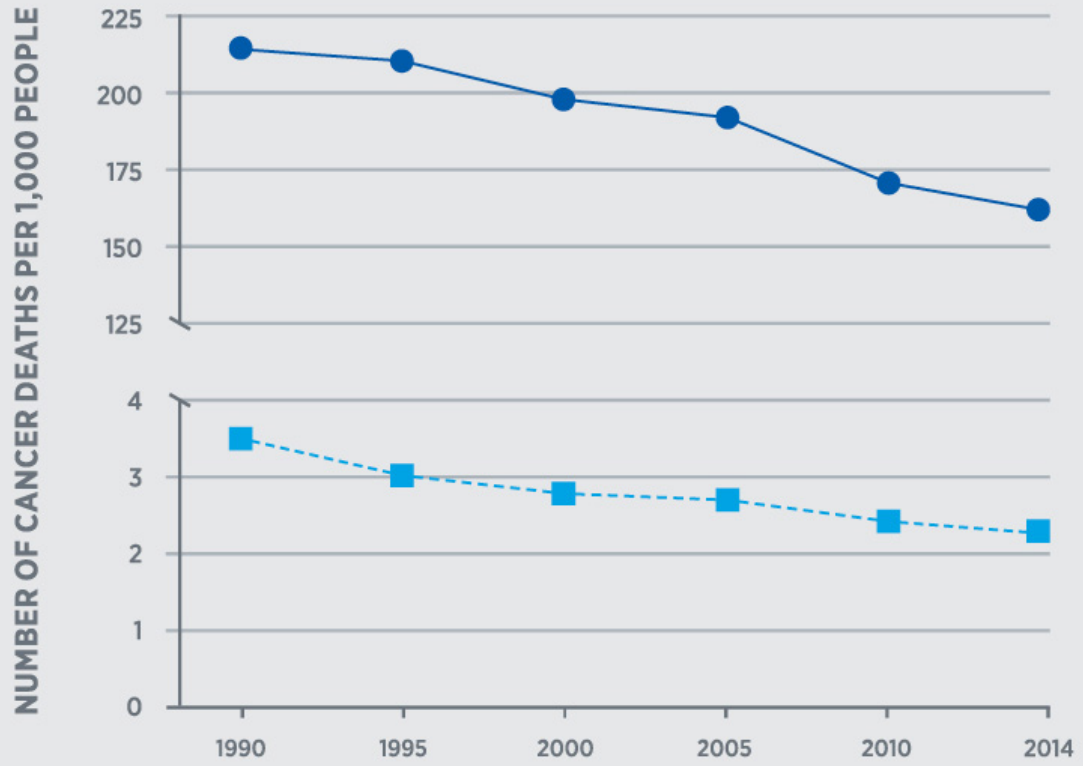
Figure 1

Making Progress against Cancer



The age-adjusted overall U.S. cancer death rates for both adults (solid blue line) and children (ages 0 to 19) (dashed blue line) have been declining steadily since the early 1990s. In 1990, there were 214.95 cancer deaths per 100,000 U.S. adults. By 2014, the last year for which these data are available, this had dropped to 161.3 per 100,000, a decline of 25 percent. During this same period, the number of childhood deaths from cancer dropped from 3.4 per 100,000 U.S. children to 2.2 per 100,000, a drop of 35 percent.

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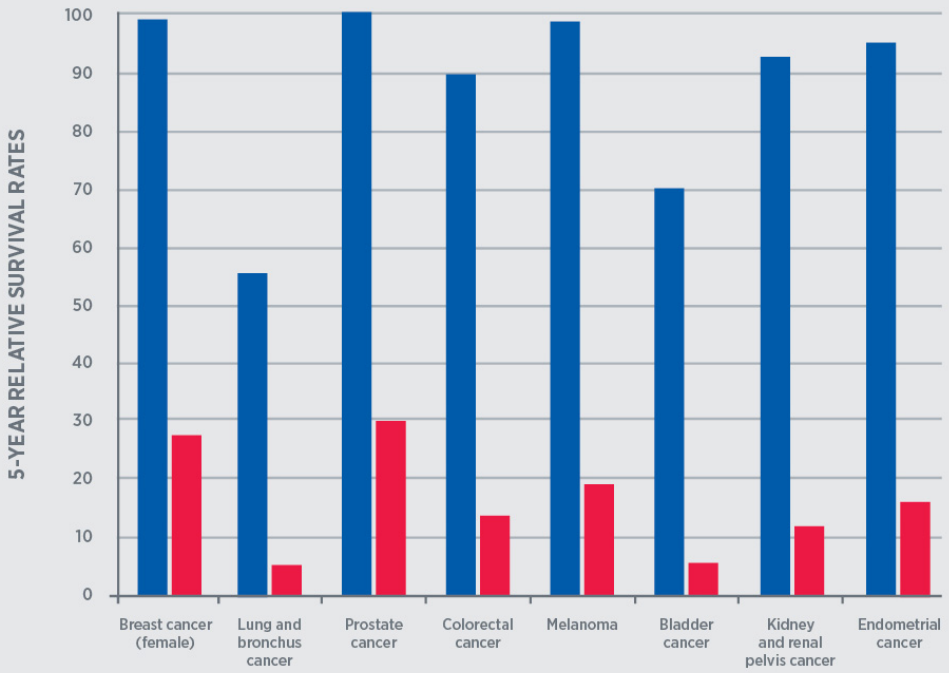
Figure 2

Cancer Poses Varying Challenges



Even though we have made significant progress against cancer, the progress has not been uniform for all types and stages of cancer. For example, as shown here, the 5-year relative survival rates for patients in the United States diagnosed with the eight most common types of solid tumor vary depending on the type of cancer diagnosed. They also vary depending on the stage of disease at diagnosis; in all cases, 5-year relative survival is substantially lower for those diagnosed when the disease has spread, or metastasized, to distant sites (red bars) than it is for those diagnosed when the disease remains confined entirely to the organ of origin (blue bars).

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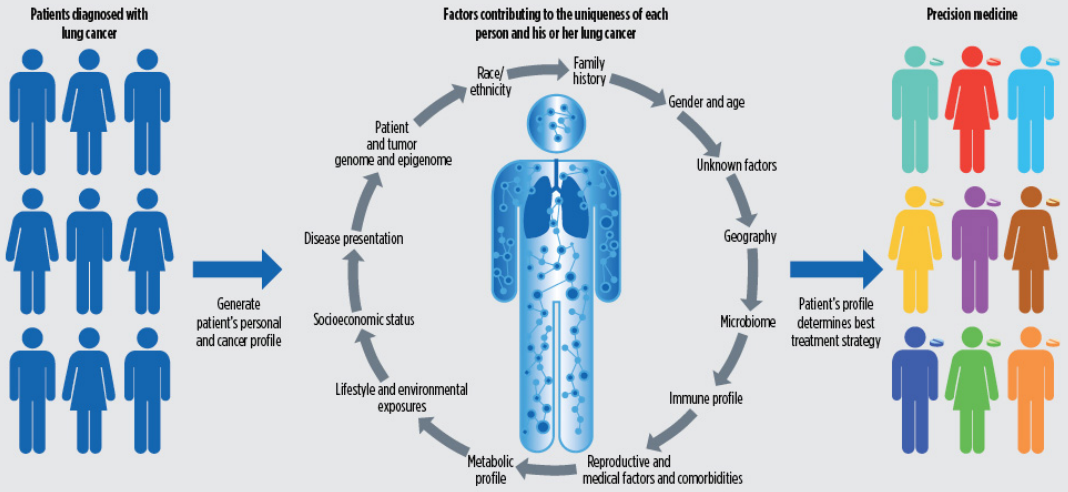
Figure 3

Precision Medicine



Precision medicine, sometimes referred to as personalized medicine, molecular medicine, or tailored therapy, is broadly defined as treating patients based on characteristics that distinguish them from other patients with the same disease. The factors that contribute to the uniqueness of each person and his or her cancer include, but are not limited to, a person's genome, the genome and epigenome of his or her cancer, disease presentation, gender, exposures, lifestyle, microbiome, and other yet-to-be-discovered features. Currently genomics is the predominant factor influencing precision medicine in oncology, but as we learn more about all of the factors we can create a more personalized profile for each patient. The figure highlights how considering all the factors that influence precision medicine can distinguish one lung cancer patient from another. Development of a personalized profile for each patient has the potential to allow physicians to tailor treatment for each patient.

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Figure 4

Risky Business

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

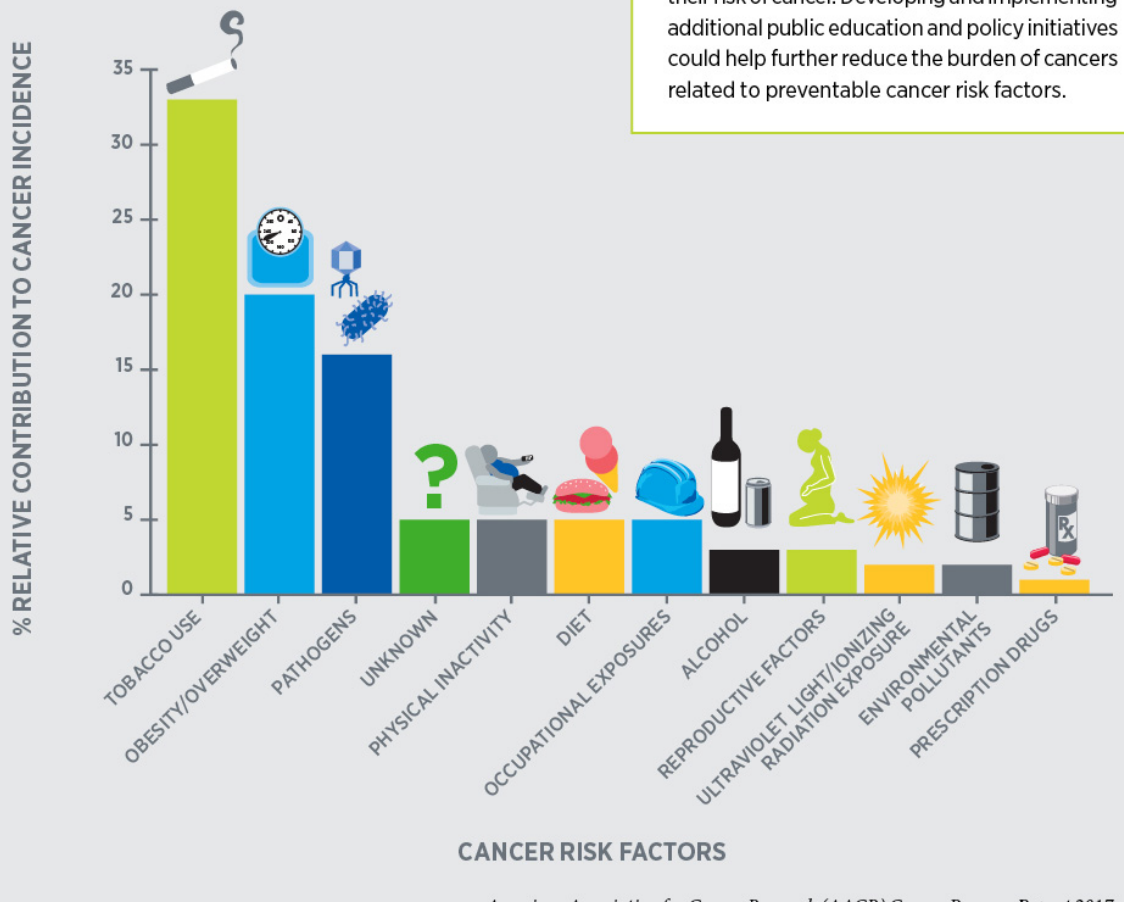

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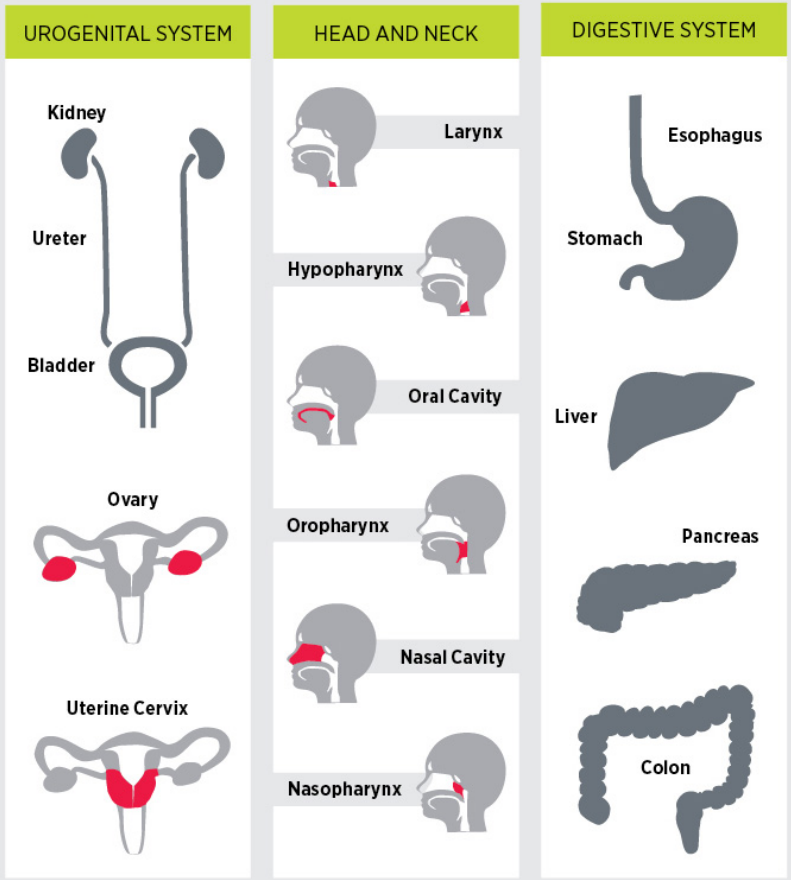
Figure 5

Beyond the Lungs: Cancers Caused by Smoking Tobacco



Smoking tobacco increases an individual's risk of developing not only lung cancer, but also 17 other types of cancer. No level of exposure to tobacco smoke is safe, including exposure to secondhand smoke, which is estimated to have resulted in more than 260,000 of the 5 million lung cancer deaths in the United States attributable to smoking from 1965 to 2014.

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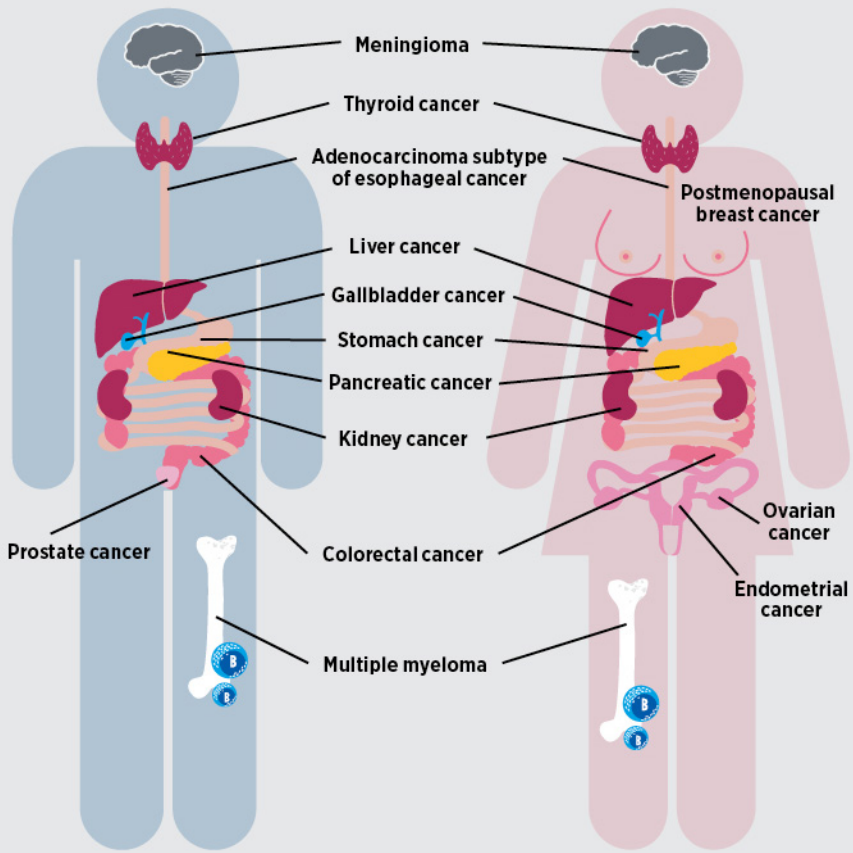
Figure 6

Weighing the Evidence: Cancers Caused by Obesity



Fourteen types of cancer—the adenocarcinoma subtype of esophageal cancer, advanced prostate cancer, meningioma, multiple myeloma, and colorectal, endometrial, gallbladder, kidney, liver, ovarian, pancreatic, stomach, thyroid, and postmenopausal breast cancers—have all been directly linked to being overweight or obese.

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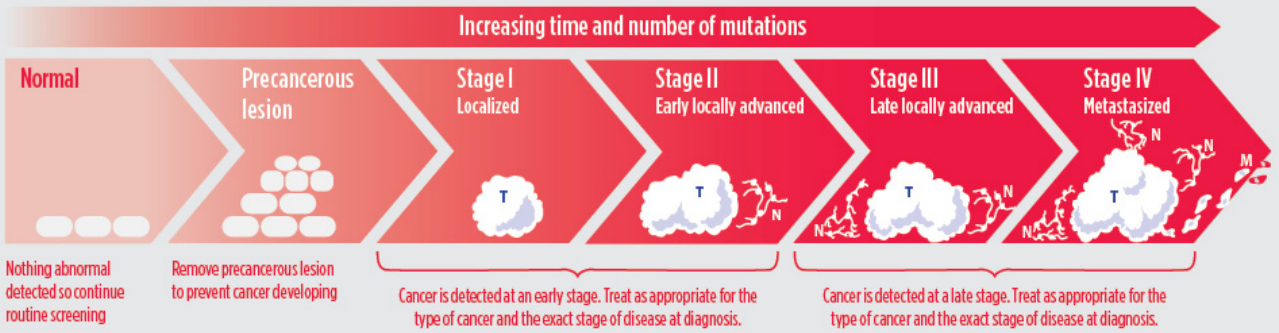
Figure 7

Cancer Screening: What Can Be Found? What Can Be Done?



Many cancers are progressive in nature. In the example depicted here, a normal cell acquires a genetic mutation that leads to its gaining precancerous characteristics. As the cell multiplies and acquires more genetic mutations, the precancerous lesion becomes increasingly abnormal. Over time, as additional genetic mutations accumulate, the precancerous lesion may evolve into a cancerous lesion (T), then spread to nearby lymph nodes (N), and, as it becomes more advanced, ultimately metastasize (M). When a person is screened for a given cancer there are many different things that can be found and many different outcomes based on the finding. For example, the screening test may show that there is no abnormality present. It may find a precancerous lesion, which can be removed before it develops into a cancerous lesion; in this situation, the screen has led to cancer prevention. It may find a cancer at an early stage of development, stage I or stage II, before it has spread and at a point at which it is more likely that the patient can be treated successfully. It may also find a cancer at a late stage of development, stage III or stage IV, when treatment is less likely to be curative. Removing a precancerous lesion or treating early-stage cancer is sometimes called cancer interception.

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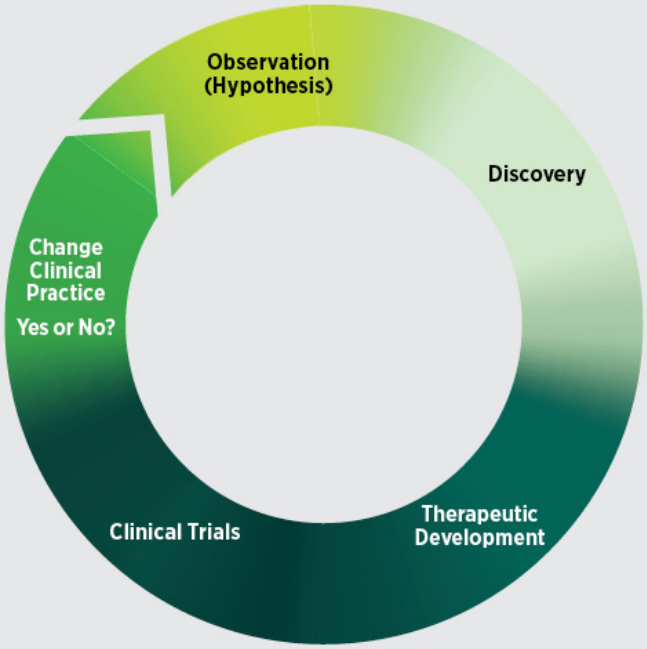
Figure 8

The Biomedical Research Cycle



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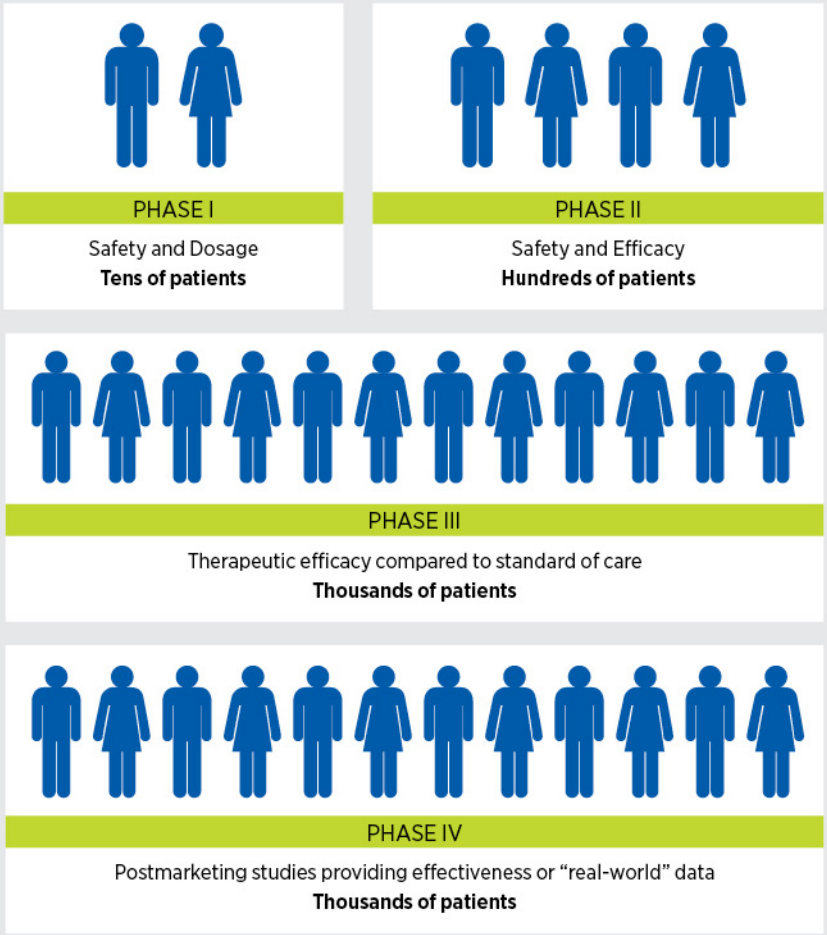
Results from any type of research can fuel biomedical research by providing observations relevant to the practice of medicine, which lead to questions, or hypotheses, that are tested in experiments during the discovery phase of research. During the discovery phase, traits unique to a disease may be uncovered, leading to the development of a potential therapeutic. Before entering clinical testing, potential therapeutics are subjected to preclinical testing to identify any toxicities and help determine initial dosing. Clinical testing is a multiphase process aimed at demonstrating the safety and efficacy of a potential therapeutic. If a therapeutic is safe and effective and is approved for use by the U.S. Food and Drug Administration (FDA), it will enter into clinical practice, where it can transform the lives of patients. Importantly, observations made during the routine use of a new therapeutic can feed back into the biomedical research cycle and further enhance the use of that therapeutic or the development of others like it. If, however, a therapeutic is not safe or effective and fails to gain FDA approval, the observations from the clinical testing still feed back into the biomedical research cycle to spur future research efforts. Because the cycle is iterative, it is constantly building on prior knowledge, and research undertaken during any part of the cycle continually powers new observations.

Figure 9

Phases of Clinical Trials



Clinical trials evaluating potential new anticancer therapeutics have traditionally been done in three successive phases, each with an increasing number of patients. Phase I studies are designed to determine the optimal dose of an investigational anticancer therapeutic, how humans process it, and potential toxicities. Phase II studies are designed to determine the initial efficacy of an investigational therapy, in addition to continually monitoring for potential toxicities. Phase III studies are large trials designed to determine therapeutic efficacy as compared to standard of care (placebos are rarely used in cancer clinical trials). When successful, the results of these trials can be used by regulators to approve new therapeutics or new indications for existing therapeutics. Phase IV studies are conducted after a therapy is provisionally approved by the FDA and provide additional effectiveness or "real-world" data on the therapy.

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Figure 10

Genomically Informed Clinical Trials

A major use of genomics in clinical research is in the design and execution of novel types of clinical trials. Two such types of trials are basket and umbrella trials. In the basket trial depicted here, one drug is being tested against a particular genetic mutation (green dots) across liver, lung, bone, colon, and stomach cancers. In the umbrella trial illustrated here, three different drugs are being tested against multiple genetic mutations (yellow, green, blue, and red dots) within lung cancer.

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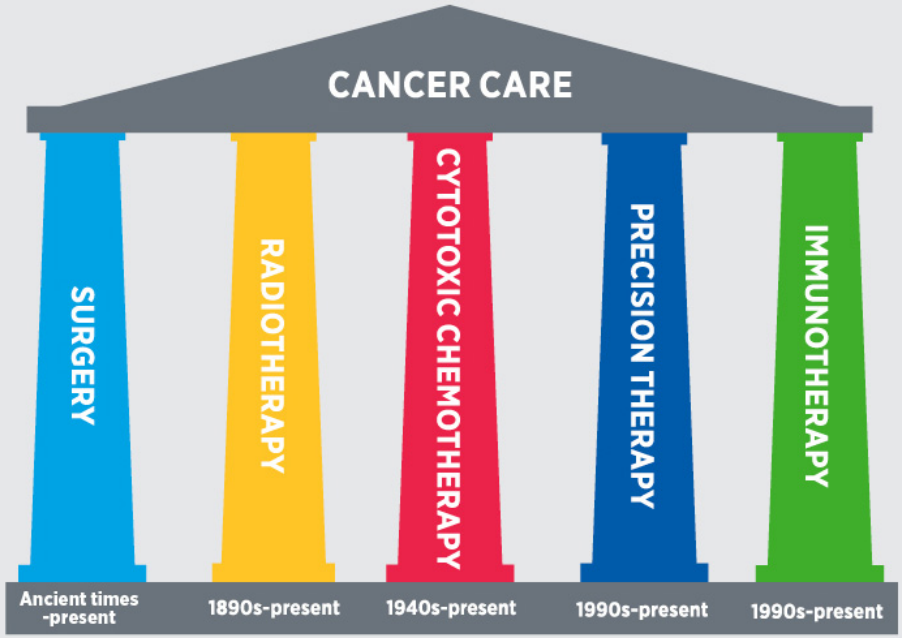
Figure 11

The Pillars of Cancer Care



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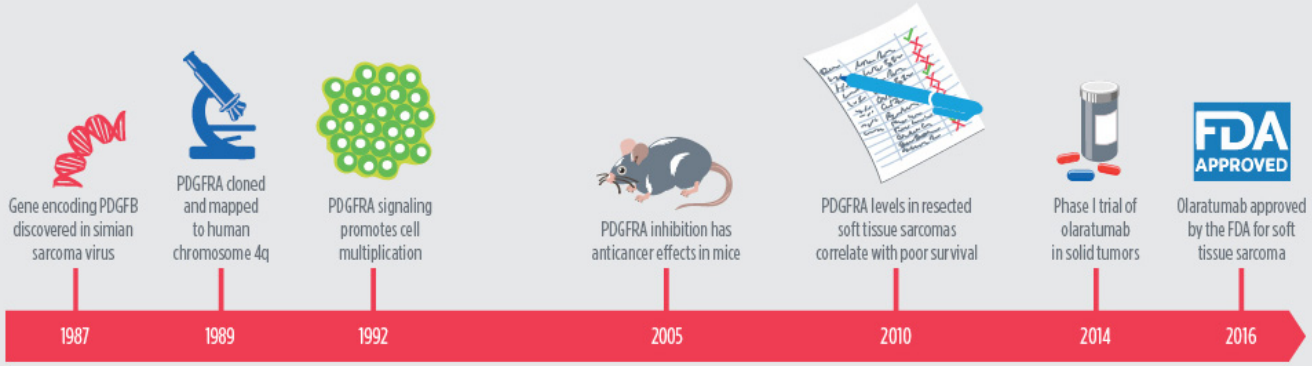
Physicians often refer to the "pillars" of cancer treatment. For thousands of years, there was one treatment pillar: surgery. In 1896, a second pillar, radiotherapy, was added. The foundations for the third treatment pillar, cytotoxic chemotherapy, were laid in the early 1940s when a derivative of nitrogen mustard was explored as a treatment for lymphoma. These three pillars—surgery, radiation, and cytotoxic chemotherapy—continue to be the mainstays of cancer care. However, in the late 1990s, the first precision therapeutics were introduced, leading to the fourth pillar, precision therapy, which continues to grow. Likewise, the late 1990s laid the groundwork for the fifth treatment pillar, immunotherapy. The number of anticancer therapeutics that form the most recent pillars of cancer care has increased dramatically in the past 5 years.

Figure 12

The Pathway to Progress against Soft Tissue Sarcoma



Olaratumab (Lartruvo) is an anticancer therapeutic that targets the protein platelet-derived growth factor receptor-alpha (PDGFRA). Its October 2016 U.S. Food and Drug Administration (FDA) approval was the culmination of almost three decades of basic, translational, and clinical research. The story began in 1987, when researchers discovered a gene they called PDGFB. Through basic research, it was determined that this protein can attach to the protein PDGFRA, triggering a signaling pathway that promotes cell multiplication. Olaratumab prevents proteins such as PDGFB from attaching to PDGFRA and thereby prevents cell multiplication.

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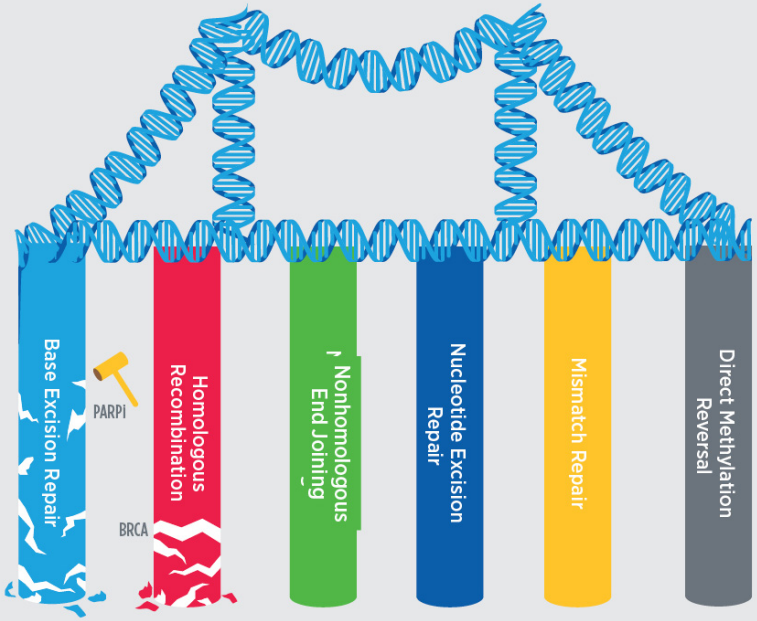
Figure 13

DNA Integrity: Bridging the Precision Gap



Basic research has shown that maintenance of DNA integrity is essential for a cell to remain healthy and maintain normal function. The integrity of DNA is constantly under threat from errors that occur during multiplication, as well as exposure to chemicals, such as those in cigarette smoke, and ultraviolet radiation from the sun. If DNA is not appropriately repaired, mutations accumulate, increasing the chance that a cell will become cancerous. As a result, cells have several interrelated pathways that they use to repair damaged DNA. The BRCA proteins are members of the homologous recombination DNA repair pathway (red support), and individuals with mutations in these proteins (BRCA label) have an increased risk of developing certain types of cancer. The PARP proteins are central to the base excision repair pathway (light blue support). Researchers have found that ovarian cancers with defective BRCA1 or BRCA2 genes are responsive to PARP inhibitors such as niraparib (Zejula) and rucaparib (Rubraca) because they lead to such pervasive DNA damage that the cancer cells die.

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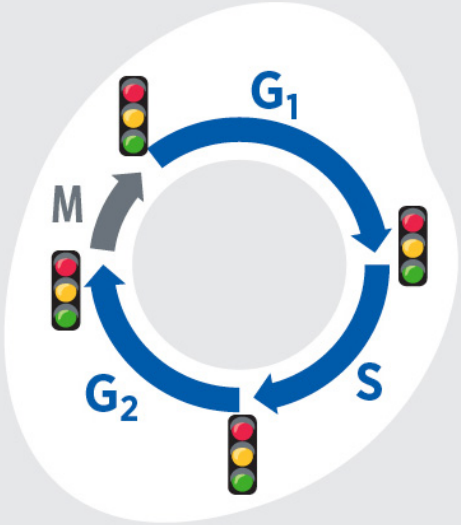
Figure 14

Checking Cell Multiplication



Cell multiplication is a cyclical process with numerous checkpoints (traffic lights) at which it can be stopped, temporarily or more permanently. The phases of the cycle between the checkpoints have different names (G1, S, G2, and M). Cyclin-dependent kinase (CDK) 4 and CDK6 are two proteins that promote passage through the checkpoint between the G1 and S phases of the cell cycle. Blocking these proteins can prevent cell multiplication. There are two anticancer therapeutics approved by the FDA that exert anticancer effects by targeting CDK4 and CDK6, palbociclib (Ibrance) and ribociclib (Kisqali). They were approved for treating certain patients with breast cancer in February 2015 and March 2017, respectively.

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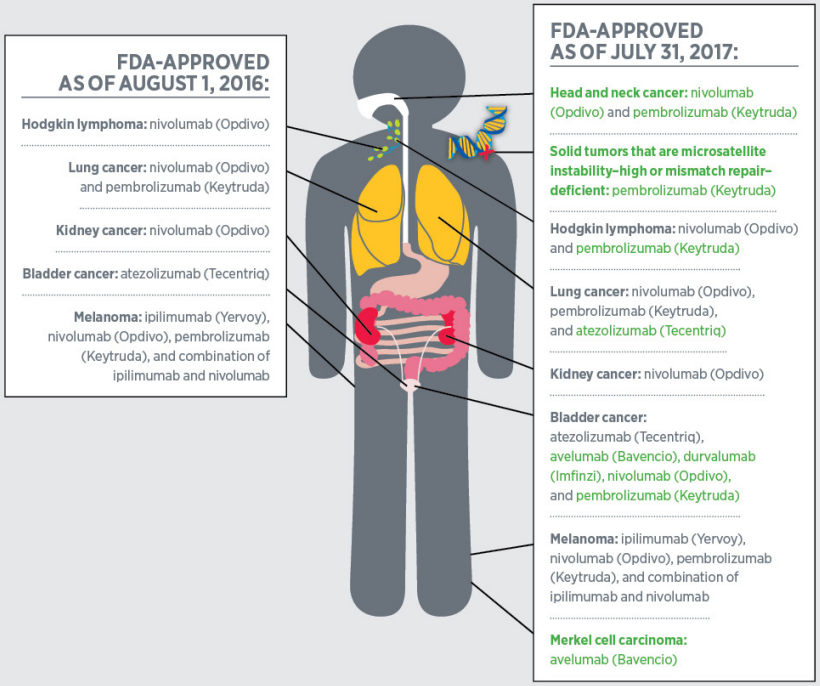
Figure 15

The Expanding Scope of Checkpoint Inhibitors



Cancer immunotherapeutics are anticancer therapeutics that work by unleashing the power of a patient's immune system to fight cancer the way it fights pathogens like the virus that causes flu and the bacterium that causes strep throat. One class of cancer immunotherapeutics works by releasing brakes on the surface of immune cells called T cells, which are naturally capable of destroying cancer cells. These revolutionary anticancer agents are called checkpoint inhibitors. In the 12 months covered by this report, August 1, 2016, to July 31, 2017, there was a dramatic increase in both the number of checkpoint inhibitors approved by the U.S. Food and Drug Administration (FDA) and the number of uses for which they are approved (shown in green). On August 1, 2016, there were four FDA-approved checkpoint inhibitors and there was one or more checkpoint inhibitor approved for treating five types of cancer. As of July 31, 2017, there were six FDA-approved checkpoint inhibitors and there was one or more checkpoint inhibitor approved for treating seven types of cancer and for treating any type of solid tumor characterized by the presence of specific molecular characteristics, or biomarkers.

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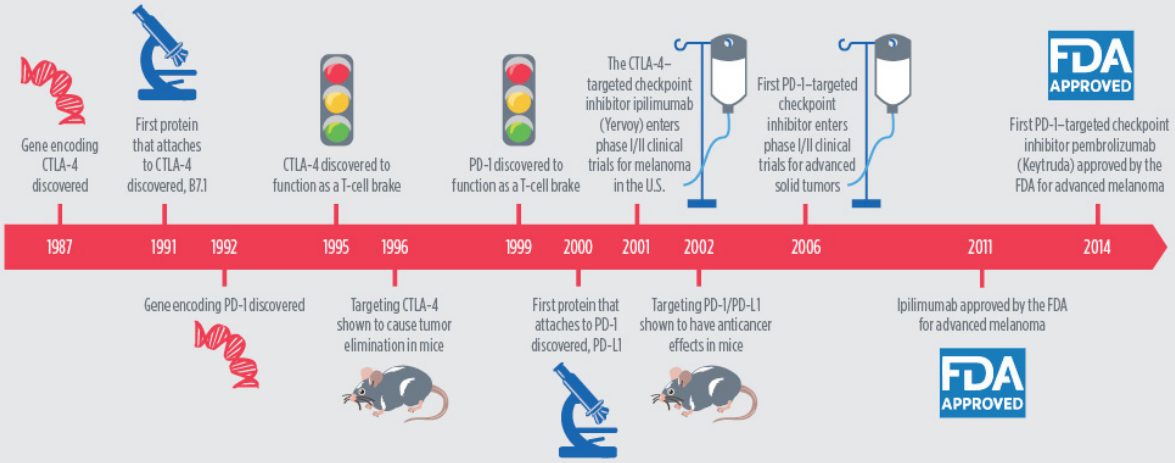
Figure 16

Stops along the Way to Developing Checkpoint Inhibitors



Checkpoint inhibitors are cancer immunotherapeutics that work by releasing brakes on the surface of cancer-fighting immune cells called T cells. The first checkpoint inhibitor to be approved by the U.S. Food and Drug Administration (FDA) was ipilimumab (Yervoy), in March 2001. It targets a brake on T cells called CTLA-4. Several other checkpoint inhibitors target a second T-cell brake called PD-1. The first of these immunotherapeutics to be approved by the FDA was pembrolizumab (Keytruda), in September 2014. More than 20 years of basic and clinical research underpinned the development of ipilimumab and pembrolizumab, starting with the discoveries of the CTLA-4 and PD-1 genes in 1987 and 1992, respectively. Other basic research milestones along the way to the FDA approvals include the identification of the brake function of CTLA-4 and PD-1, identification of the proteins that attach to and trigger the brake function of CTLA-4 and PD-1, and the demonstration that immunotherapeutics targeting these brakes can protect them from being triggered.

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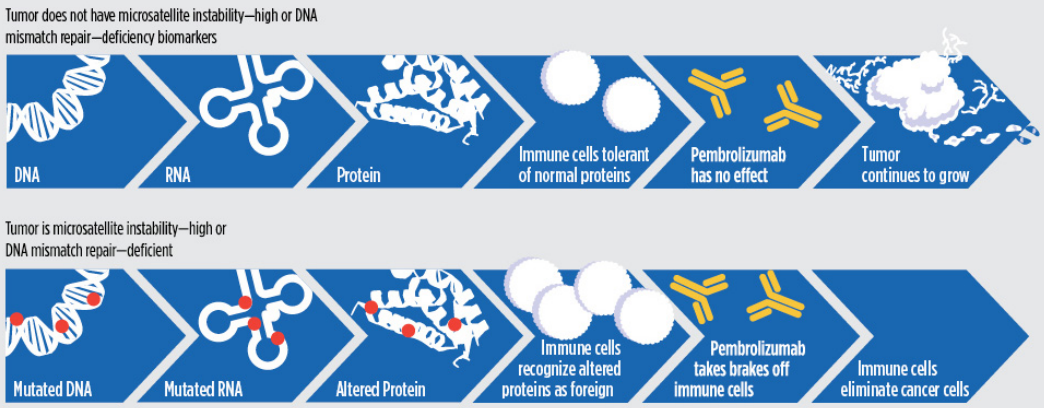
Figure 17

More Precisely Identifying Tumors Likely to Respond to Checkpoint Inhibitors



Precision medicine is broadly defined as treating a patient based on characteristics that distinguish that patient from other patients with the same disease. The U.S. Food and Drug Administration (FDA) accelerated approval of pembrolizumab (Keytruda) for the treatment of any solid tumor identified to be microsatellite instability–high or DNA mismatch–repair deficient is an example of precision immunotherapy. The scientific rationale underpinning this approval was the result of dedicated researchers integrating scientific discoveries in the fields of immunology and cancer biology to develop an understanding of why microsatellite instability–high and DNA mismatch–repair deficiency are effective biomarkers for the use of pembrolizumab. Cancer cells with these biomarkers have many mutations in their DNA. These mutations give rise to altered proteins, which are recognized as abnormal, or foreign, to cancer-fighting immune cells called T cells. These T cells are spurred into action when the PD-1 brake that is preventing them from eliminating cancer cells is released by pembrolizumab. In cancer cells that are not microsatellite instability–high and DNA mismatch–repair deficient, there are dramatically fewer DNA mutations and, therefore, few altered proteins. The immune cells in this situation accept the protein landscape in the tumor as normal and are unlikely to be spurred into action by pembrolizumab. Motivated by the strong scientific rationale for using microsatellite instability–high and DNA mismatch–repair deficiency as biomarkers for pembrolizumab treatment, researchers are currently testing whether these biomarkers are also effective for identifying patients likely to benefit from treatment with other PD-1/PD-L1–targeted checkpoint inhibitors including nivolumab (Opdivo).

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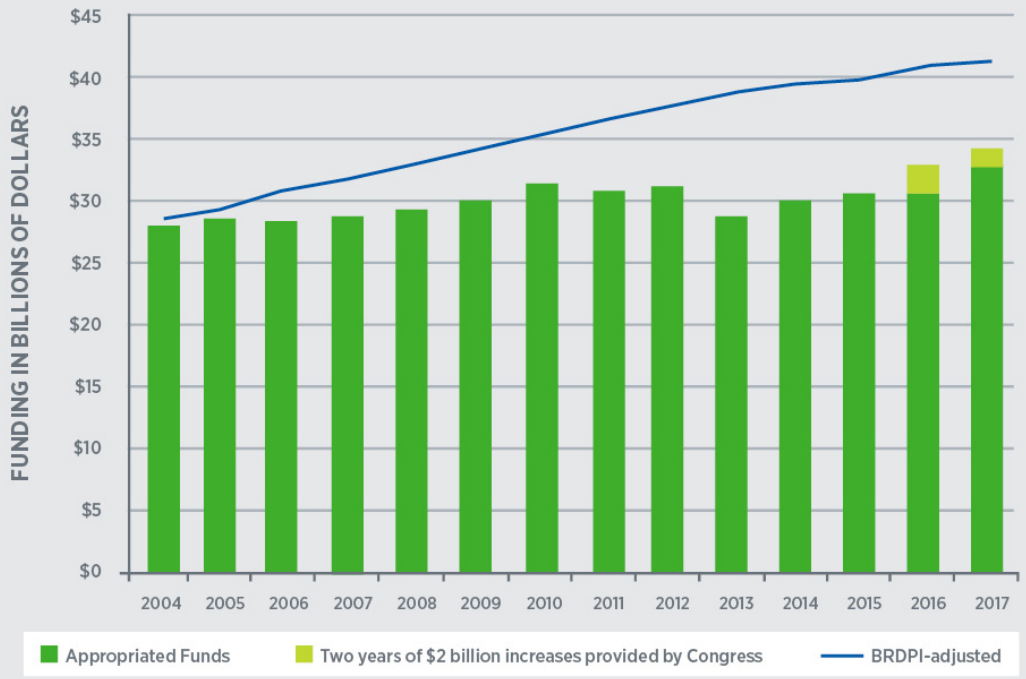
Figure 18

Putting the NIH Budget Back on Track



The biomedical research and development price index (BRDPI) reflects the rising cost of personnel, supplies, and equipment needed to conduct biomedical research. From 2004 to 2015, the National Institutes of Health (NIH) budget did not keep pace with BRDPI. Thanks to Congressional leaders, the NIH received two consecutive years of significant funding increases in fiscal year (FY) 2016 and FY 2017, which have resulted in the first real budget growth in more than a decade. Continued support is required to close the gap created by years of budgets that failed to keep up with inflation and to ensure major progress against cancer and other diseases.

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