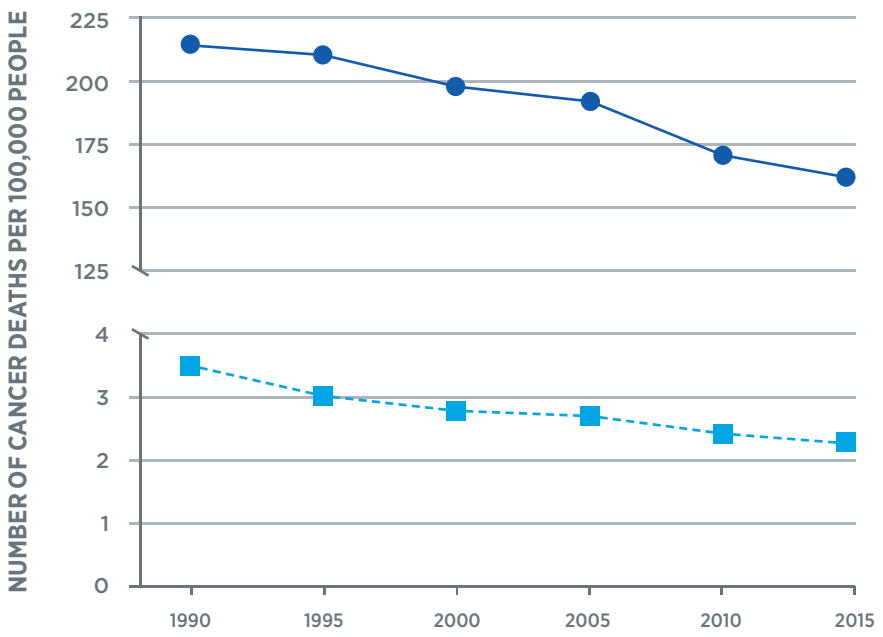
FIGURE 1

MAKING PROGRESS AGAINST CANCER



The age-adjusted overall U.S. cancer death rates for adults (—●—), and children and adolescents (ages 0 to 19) (- -■- -) have been declining steadily since the early 1990s. In 1990, there were 214.95 cancer deaths per 100,000 U.S. adults. By 2015, the most recent year for which these data are available, this had dropped to 158.68 per 100,000, a decline of 26 percent. During this period, the number of deaths from childhood cancer dropped from 3.4 per 100,000 U.S. children and adolescents to 2.3 per 100,000, a drop of 32 percent (3).

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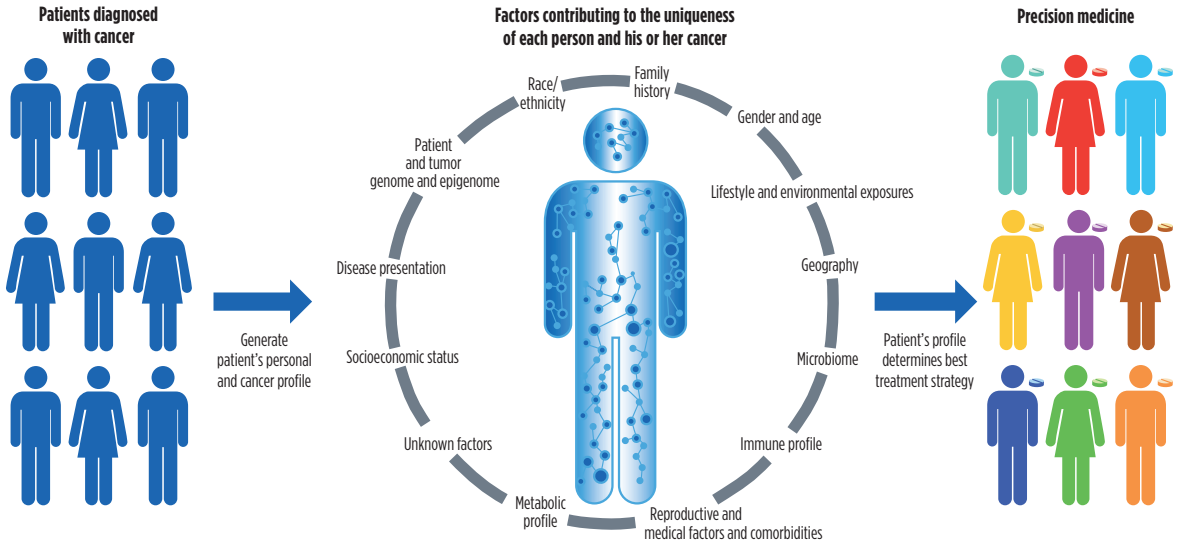
FIGURE **2**

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, comorbidities, and other yet-to-be-discovered features. Currently, genomics is the predominant factor influencing precision medicine in oncology, but as we learn more about additional factors we can create a more personalized profile for each patient. The figure highlights how factors that influence precision medicine can be utilized to stratify a group of patients with a site-specific cancer. Development of a personalized profile for each patient has the potential to allow physicians to tailor treatment for each patient.

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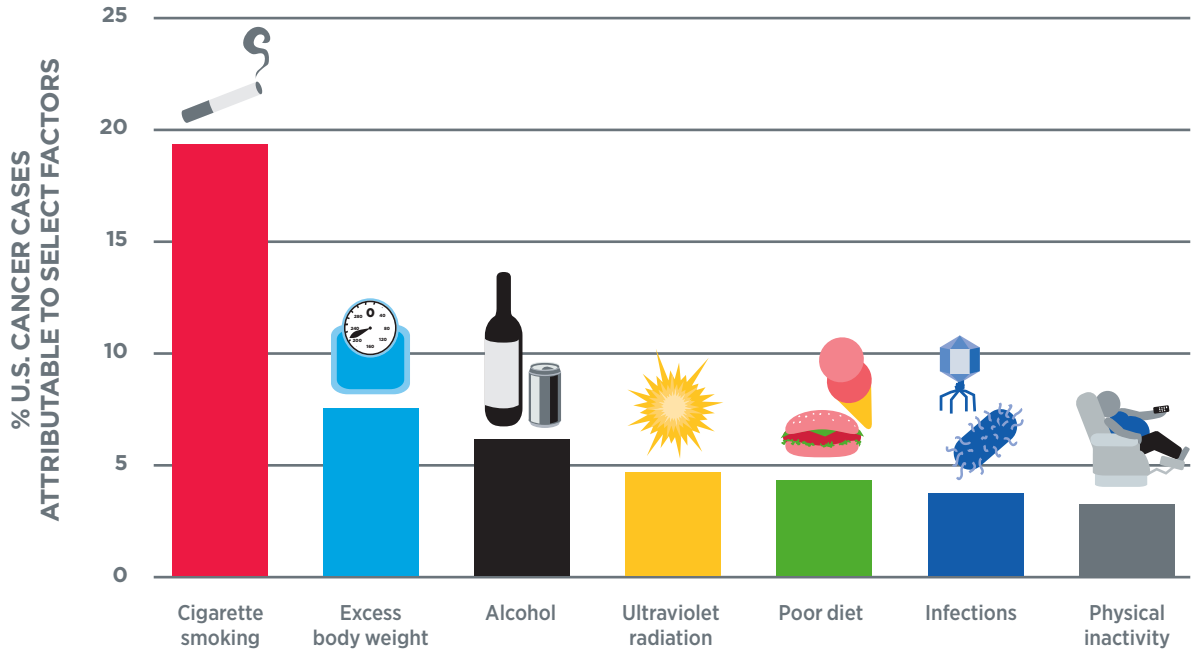
FIGURE 3

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.

Adapted from (39).

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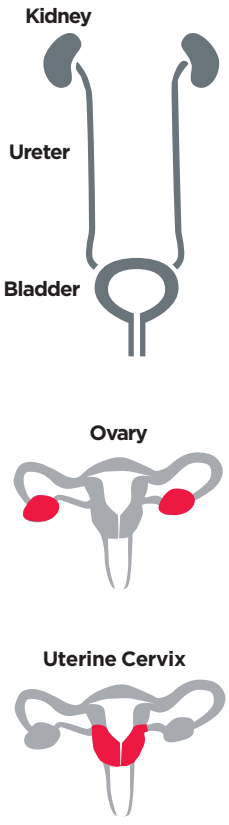
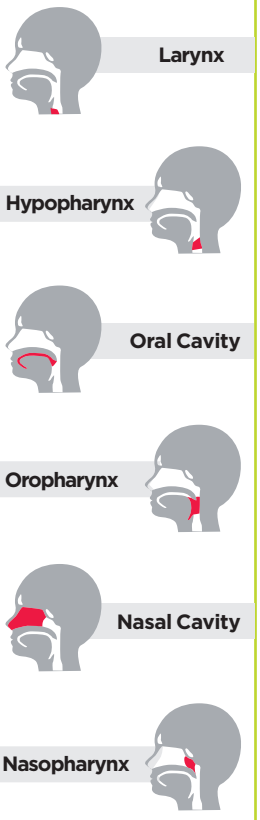
FIGURE **4**

BEYOND THE LUNGS: CANCERS CAUSED BY SMOKING TOBACCO

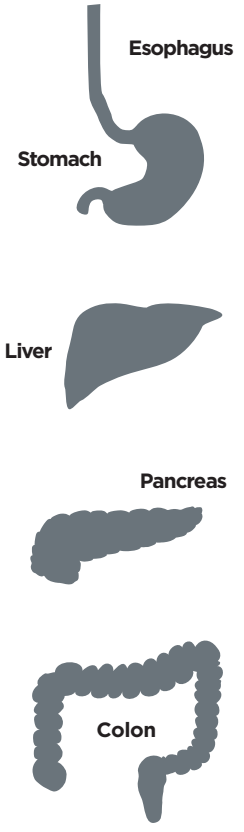
UROGENITAL SYSTEM



HEAD AND NECK



DIGESTIVE SYSTEM



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.

Adapted from (1).

LUNG AND BRONCHUS

HEMATOPOIETIC SYSTEM

Acute myeloid leukemia

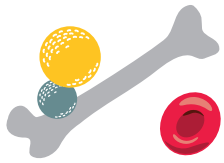


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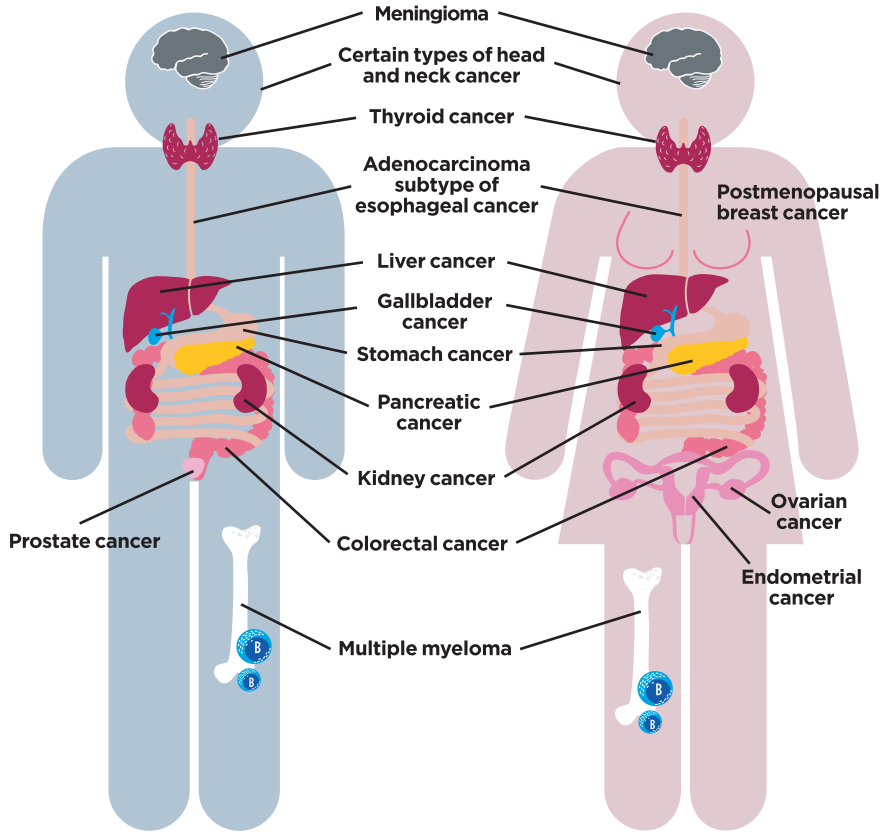
FIGURE **5**

WEIGHING THE EVIDENCE: CANCERS CAUSED BY OBESITY



Fifteen types of cancer—the adenocarcinoma subtype of esophageal cancer, certain types of head and neck 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 (72,73).

Adapted from (31).

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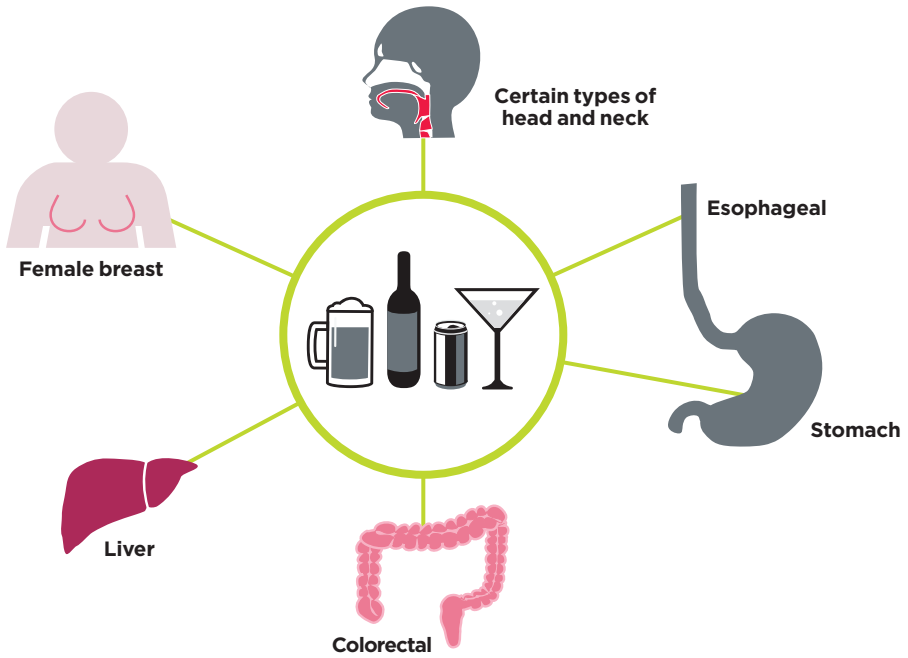
FIGURE 6

ALCOHOL AND CANCER RISK



Consumption of alcohol increases an individual's risk of developing six types of cancer—certain types of head and neck cancer, esophageal squamous cell carcinoma, and breast, colorectal, liver, and stomach cancers (85).

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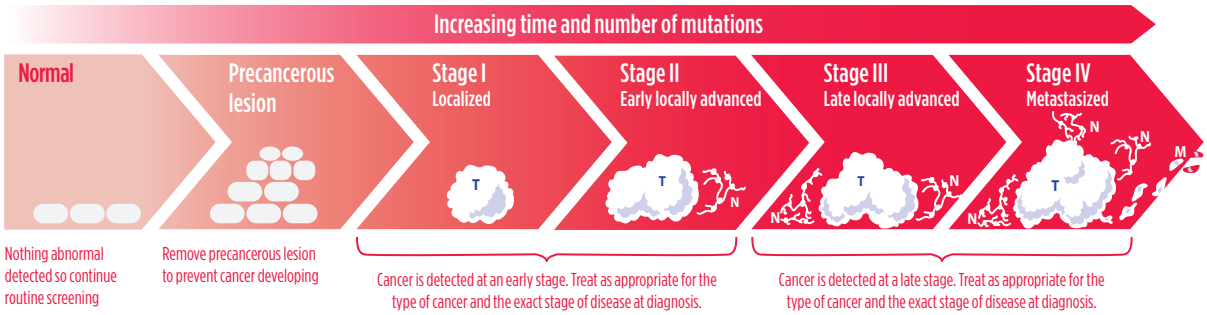
FIGURE **7**

CANCER SCREENING: WHAT CAN BE FOUND? WHAT CAN BE DONE?

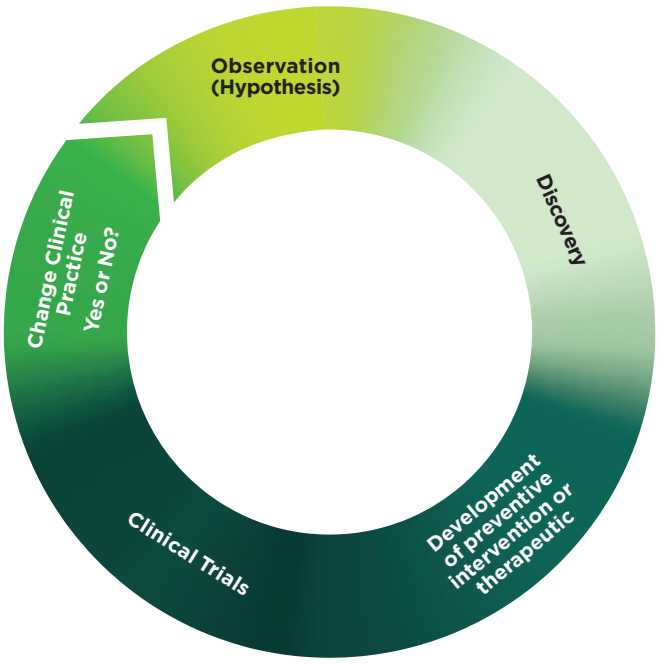


Many cancers are progressive in nature. In the example depicted here, a normal cell contains an inherited genetic mutation or an acquired one. At this point, there is nothing that can be detected with cancer screening tests but the cell is predisposed to becoming cancerous. As the cell multiplies and acquires more mutations, it gains precancerous characteristics and an increasingly abnormal precancerous lesion becomes detectable. Over time, as additional mutations accumulate, the precancerous lesion evolves into a cancerous lesion (T), then it spreads to nearby lymph nodes (N), and, as it becomes more advanced, ultimately it metastasizes (M). When a person is screened for a given cancer there are several different things that can be found, and different outcomes based on the finding. For example, the screening test may show that there is no abnormality present; in this situation, the person should continue routine screening. It may detect a precancerous lesion, which can be removed or treated; in this situation, the screen has led to the prevention of a cancerous lesion developing. 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 also may 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.

Adapted from (36).

FIGURE **8**

THE BIOMEDICAL RESEARCH CYCLE



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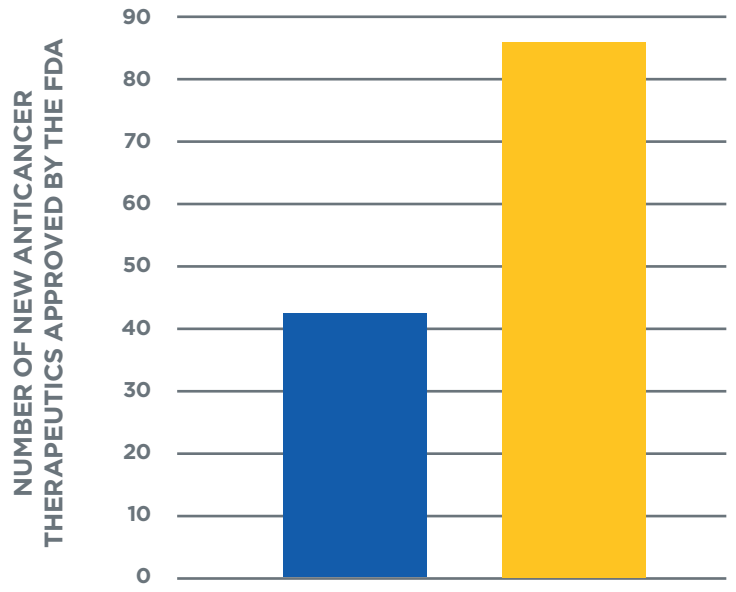
Results from any type of research can fuel the biomedical research cycle by providing observations relevant to the practice of medicine, which lead to questions, or hypotheses, that are tested in experiments during the discovery phase of research. During the discovery phase, traits unique to a disease may be uncovered, leading to the development of a potential preventive intervention or therapeutic (see sidebar on **Developing Preventive Interventions and Therapeutics**, p. XX). Before entering clinical testing, potential preventive interventions or therapeutics undergo 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 preventive intervention or therapeutic. If an agent is safe and effective and is approved for use by the U.S. Food and Drug Administration (FDA), it will enter clinical practice. Importantly, observations made during the routine use of a new preventive intervention or therapeutic can feed back into the biomedical research cycle and further enhance the use of that agent or the development of others like it. If, however, a preventive intervention or 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.

Adapted from (31).

FIGURE **9**

DOUBLE THE PROGRESS



The pace at which research discoveries are being converted to new anticancer therapeutics has been accelerating in recent years, as illustrated by the fact that the number of new anticancer therapeutics approved by the US Food and Drug Administration (FDA) from 2009 to 2018* (yellow bar) was more than double the number approved by the agency in the decade before (1999–2008) (blue bar); 86 versus 42.

Data obtained from (121) and https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugInnovation/default.htm

**Till July 31, 2018*

American Association for Cancer Research (AACR) Cancer Progress Report 2018

FIGURE **10**

THE TRADITIONAL APPROACH TO CANCER CLINICAL TRIALS

Cancer clinical trials evaluating potential new preventive interventions and 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 agent, how humans process it, and potential toxicities. Phase II studies are designed to determine the initial efficacy of an agent, in addition to continually monitoring for potential toxicities. Phase III studies are large trials designed to determine efficacy as compared to standard of care (placebos are rarely used in cancer treatment clinical trials). When successful, the results of these trials can be used by regulators to approve new preventive interventions or therapeutics, or new indications for existing agents. Phase IV studies are conducted after an agent is provisionally approved by the FDA and provide additional effectiveness or "real-world" data on the agent.

Adapted from (18).

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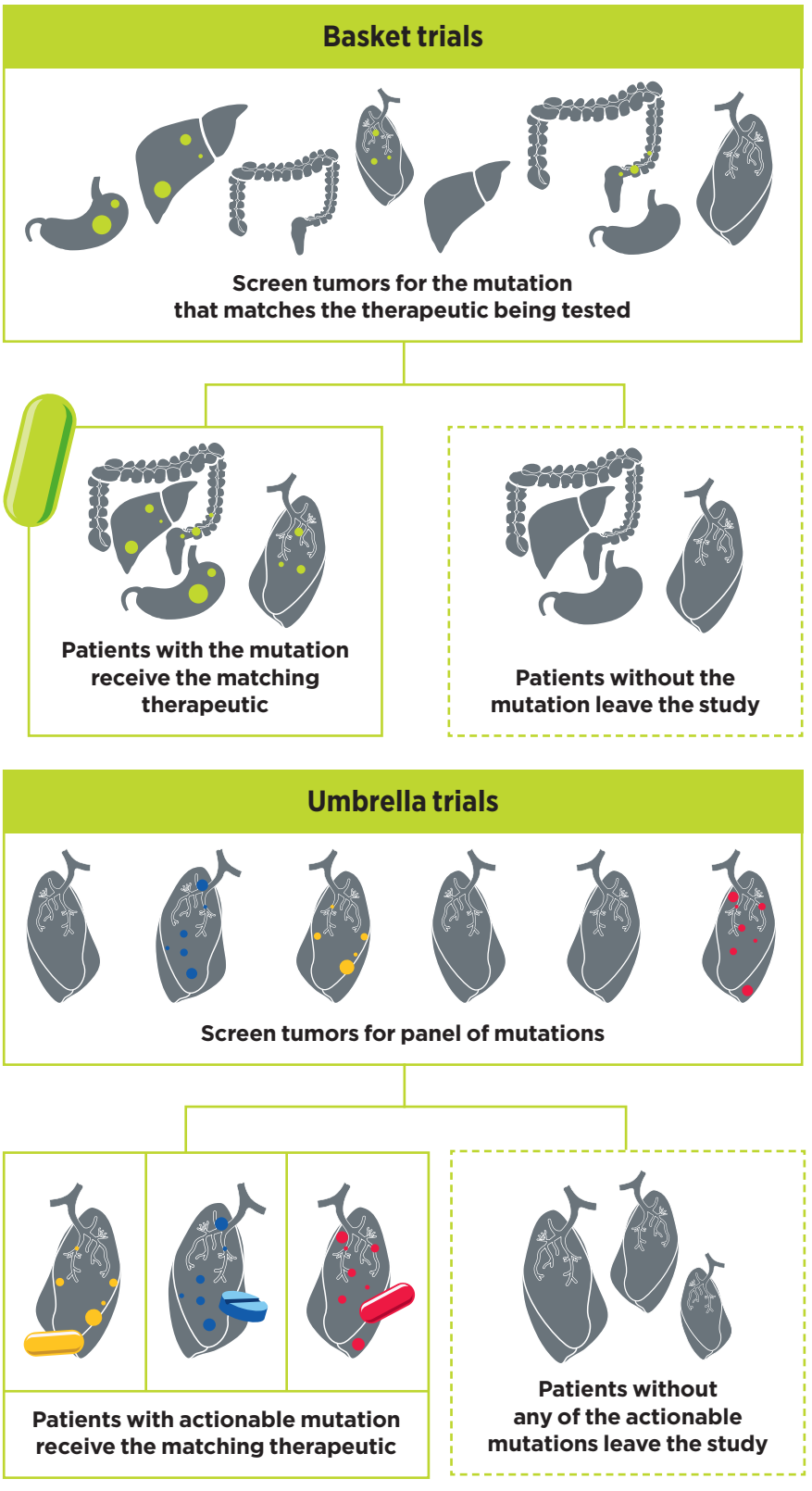
FIGURE 11

MASTERING CLINICAL TRIAL DESIGN



Recent advances in our understanding of cancer biology have led to new ways of designing and conducting clinical trials. One of the new approaches is to use a master protocol to answer multiple questions within a single overall clinical trial. Two types of master protocol clinical trial are basket and umbrella trials. These trials allow the development of new anticancer therapeutics to be streamlined. The right therapeutics are matched with the right patients earlier, which reduces the number of patients who need to be enrolled in the trial before it is determined whether or not the anticancer therapeutic being evaluated is safe and effective, and/or decreases the length of time it takes for a new anticancer therapeutic to be tested and made available to patients if the trial shows it is safe and effective. In the basket trial depicted here, one drug is being tested against a particular genetic mutation (green dots) across liver, lung, colon, and stomach cancers. In the umbrella trial illustrated here, three different drugs are being tested against multiple genetic mutations (yellow, blue, and red dots) within lung cancer.

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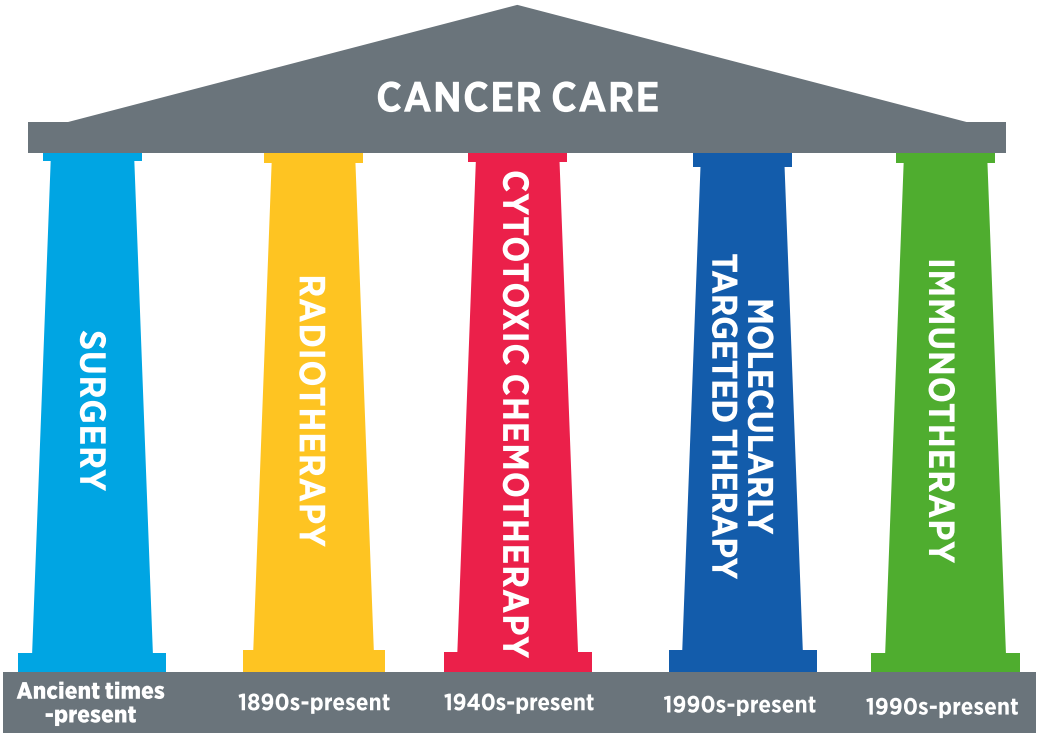
FIGURE 12

THE PILLARS OF CANCER CARE

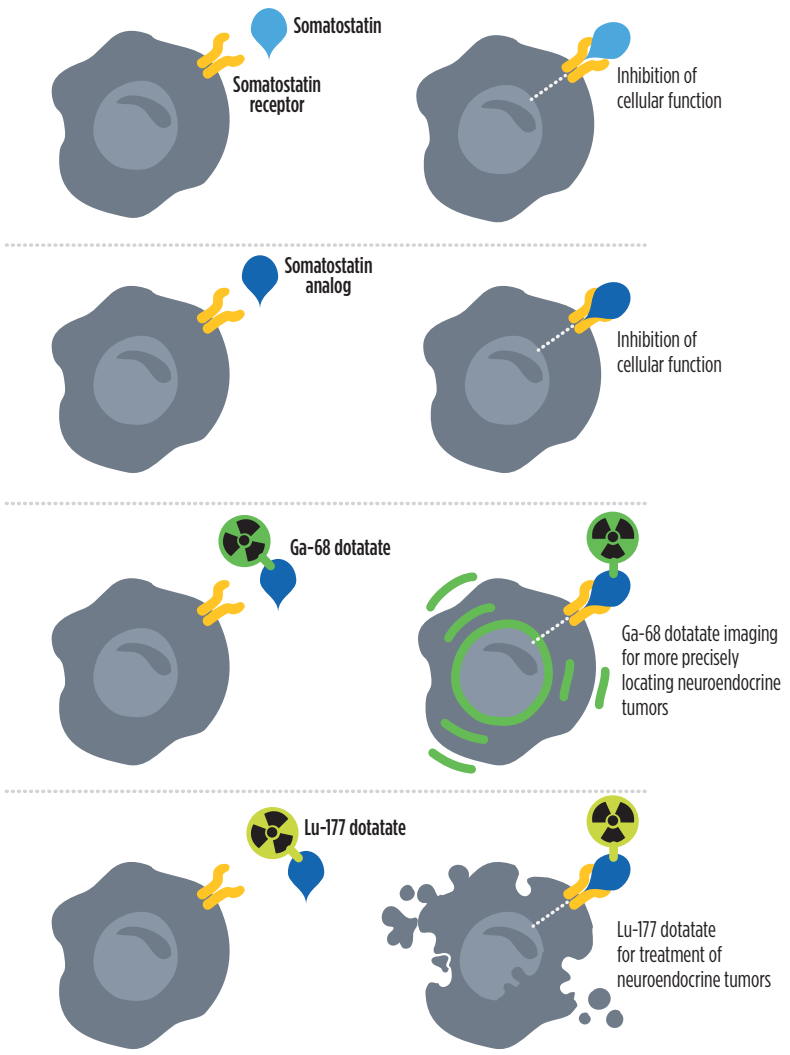


Physicians often refer to the "pillars" of cancer treatment. For many years, there was one treatment pillar: surgery. In 1896, a second pillar, radiotherapy, was added. The foundations for the third treatment pillar, cytotoxic chemotherapy, were laid in the early 1940s when a derivative of nitrogen mustard 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 molecularly targeted therapeutics were introduced, leading to the fourth pillar, molecularly targeted 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 two pillars of cancer care continues to increase every year.

Adapted from (31).

FIGURE 13

HARNESSING KNOWLEDGE IN MULTIPLE WAYS



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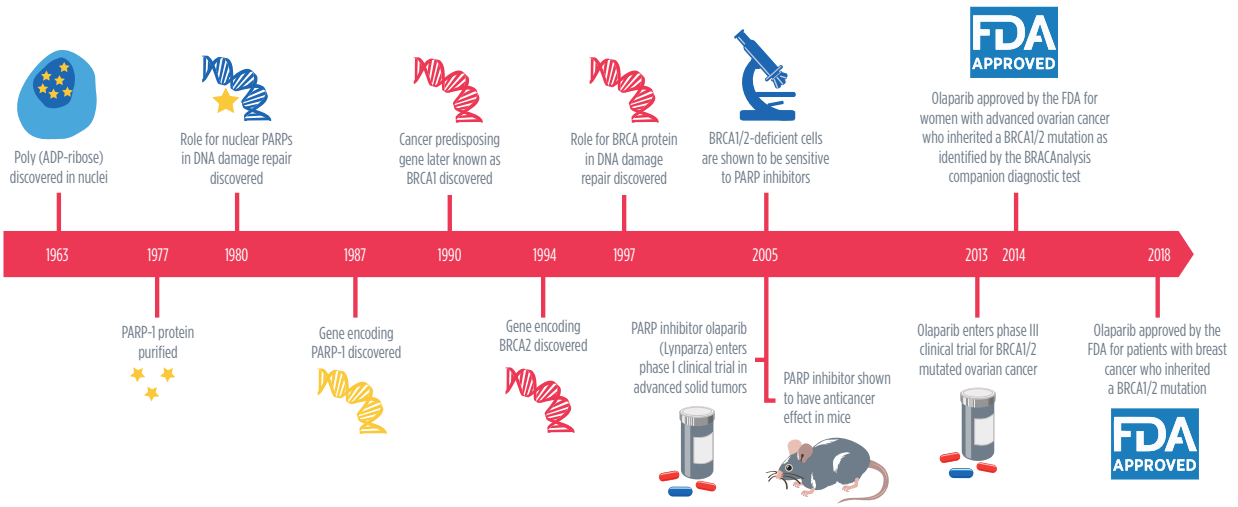
Since the discovery of somatostatin in 1973, researchers have learned much about the hormone, its natural biological functions, and the ways in which it exerts these functions (154). They have learned that the main function of somatostatin is to inhibit the function of cells. It does this by attaching to proteins called somatostatin receptors on the surface of cells, sending signals that suppress the functions of the cells. Research has also shown that most neuroendocrine tumors have somatostatin receptors on the surface. This body of knowledge was first harnessed to develop agents that mimic the effects of somatostatin, so-called somatostatin analogues. These agents have been used to treat patients with neuroendocrine tumors since the late 1980s. This provided the foundation for the development of radiolabeled somatostatin analogues. A somatostatin analogue linked to the radionuclide gallium (Ga) 68 was approved by the U.S. Food and Drug Administration (FDA) in June 2016 for use with positron emission tomography–computed tomography (PET–CT) to help physicians more precisely locate neuroendocrine tumors in the body during diagnosis (36). Then, in January 2018, the FDA approved a second radiolabeled somatostatin analogue, lutetium (Lu) 177 dotatate (Lutathera), for treating patients with gastroenteropancreatic neuroendocrine tumors.

FIGURE **14**

RESEARCH MILESTONES ON THE ROAD TO DEVELOPING OLAPARIB



Olaparib (Lynparza) is a molecularly targeted therapeutic that was approved for treating women with advanced ovarian cancer who have inherited a cancer-associated mutation in the BRCA1 or BRCA2 gene (BRCA1/2 mutation) in December 2014. In February 2018, it was approved for treating patients with HER2-negative, metastatic breast cancer who have inherited a cancer-associated BRCA1/2 mutation. Olaparib targets poly ADP-ribose polymerase (PARP) proteins. Five decades of basic and clinical research underpinned the development of olaparib, starting with the 1963 discovery that poly ADP-ribose could be generated by an enzyme in the nucleus. Other research milestones along the way to the FDA approvals include the purification of the PARP-1 protein, the discovery that PARP and BRCA proteins are involved in repairing damaged DNA, the discoveries of the PARP-1, BRCA1, and BRCA2 genes, and the demonstration that BRCA1/2-deficient cells and tumors are sensitive to PARP inhibitors. Data from (170,171).

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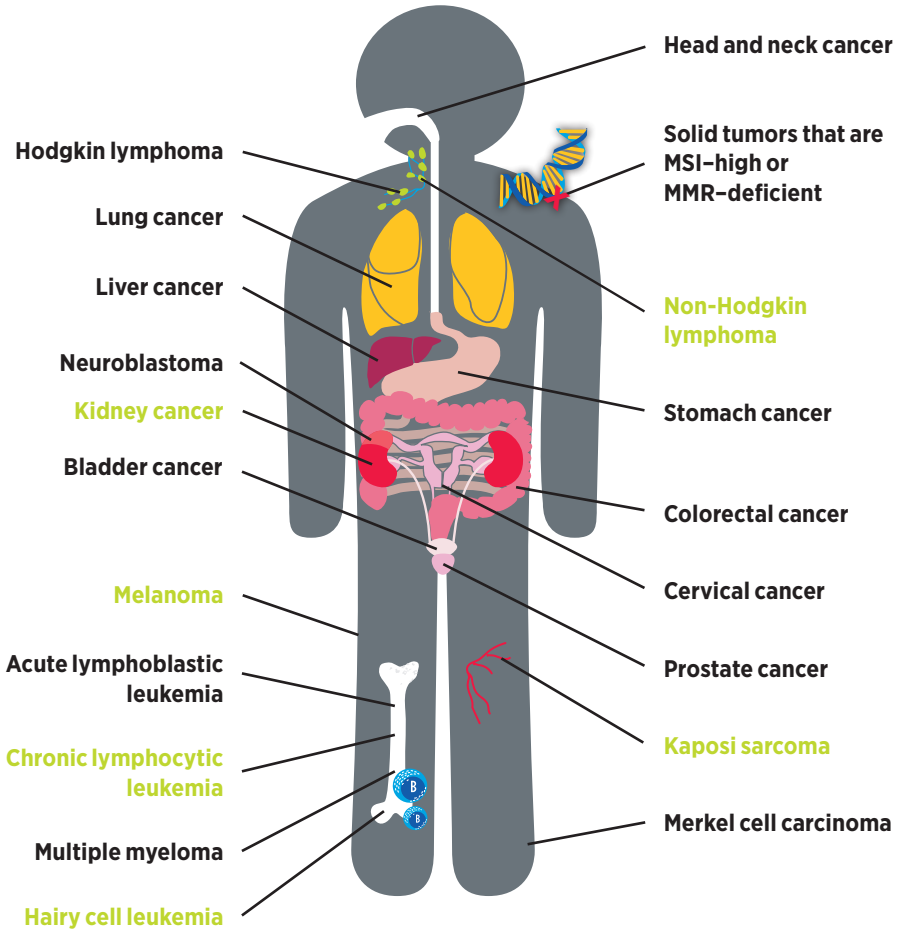
FIGURE **15**

THE EXPANDING SCOPE OF IMMUNOTHERAPY

As of July 31, 2018,
immunotherapeutics were FDA approved for treating certain patients with:



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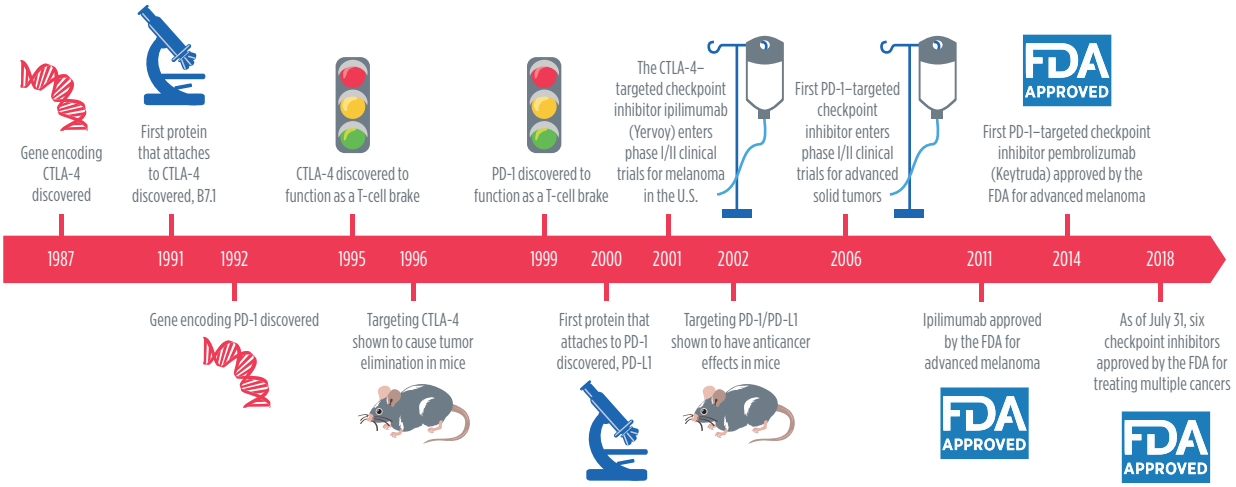
Cancer immunotherapy refers to anticancer therapeutics that work by unleashing the power of a patient's immune system to fight cancer the way it fights pathogens such as the virus that causes flu and the bacterium that causes strep throat. In the 10 years since July 31, 2008, there has been a dramatic increase in both the number of immunotherapeutics approved by the U.S. Food and Drug Administration (FDA) and the number of uses for which they are approved. On August 1, 2008, one or more immunotherapeutics were approved for treating just six types of cancer (shown in green). As of July 31, 2018, one or more immunotherapeutics were approved for treating 19 types of cancer and for treating any type of solid tumor characterized by the presence of specific molecular characteristics, or biomarkers.

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 2011. 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 (187,188). Other basic research milestones along the way to the FDA approvals include the identification of the brake function of CTLA-4 and PD-1 (189–191), identification of the proteins that attach to and trigger the brake function of CTLA-4 and PD-1 (192,193), and the demonstration that immunotherapeutics targeting these brakes can protect them from being triggered (188,194).

Adapted from (39).

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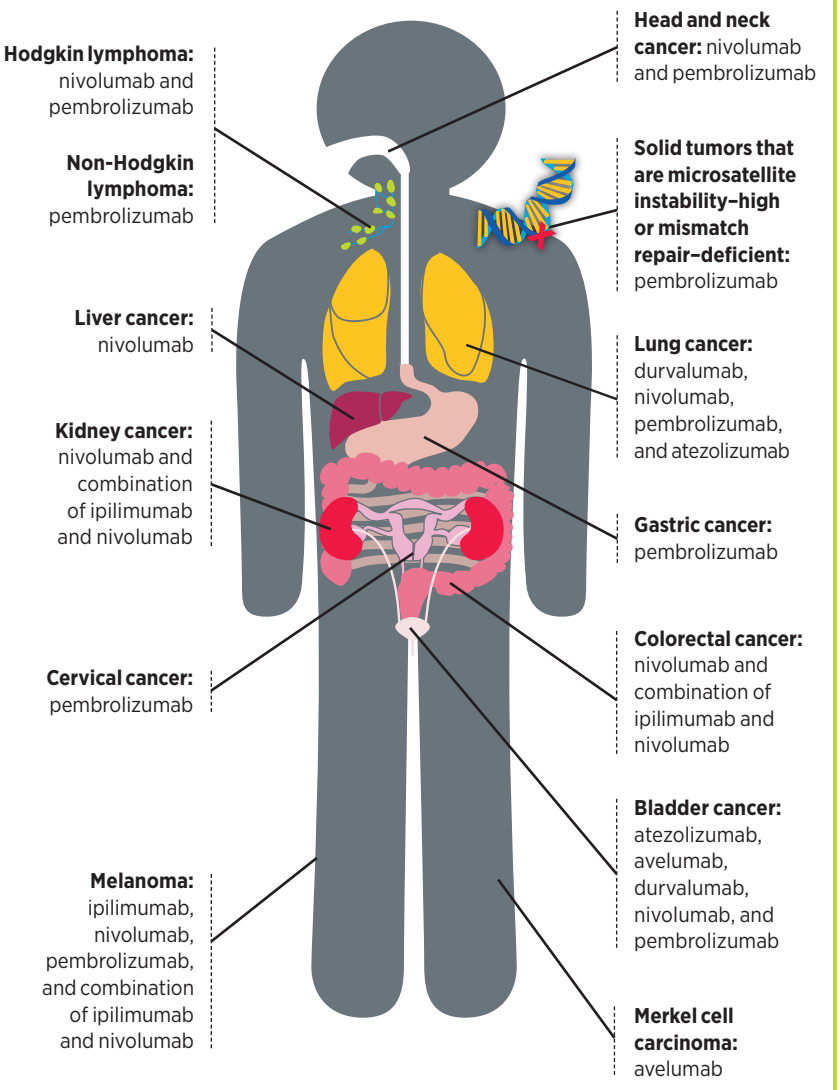
FIGURE **17**

GOING DEEP WITH CHECKPOINT INHIBITORS



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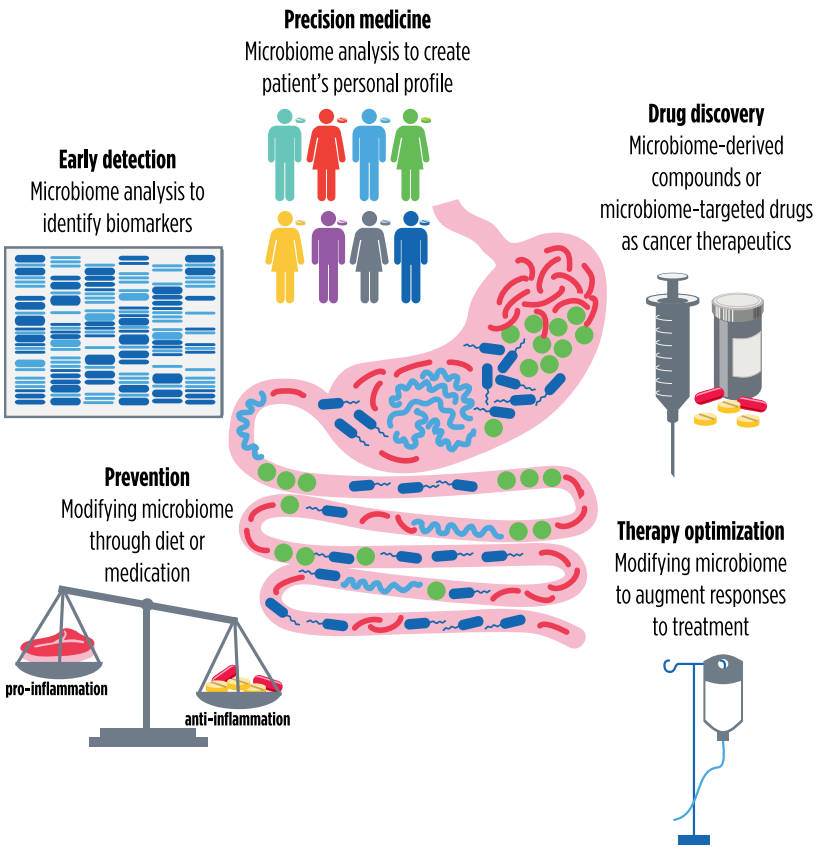
Checkpoint inhibitors are cancer immunotherapeutics that work by releasing brakes on the surface of immune cells called T cells, which are naturally capable of destroying cancer cells. The first checkpoint inhibitor to be approved by the U.S. Food and Drug Administration (FDA) was ipilimumab (Yervoy), in March 2011, for metastatic melanoma. Three-and-a-half years passed before another checkpoint inhibitor was approved, pembrolizumab (Keytruda), again for metastatic melanoma. Since then, another four checkpoint inhibitors have been approved by the FDA, atezolizumab (Tecentriq), avelumab (Bavencio), durvalumab (Imfinzi), and nivolumab (Opdivo). In addition, the FDA has expanded the number of cancer types for which there is at least one checkpoint inhibitor approved. The broad utility of these groundbreaking immunotherapeutics is highlighted by the fact that as of July 31, 2018, one or more checkpoint inhibitors were approved for treating 12 types of cancer and for treating any type of solid tumor characterized by the presence of specific molecular characteristics. In addition, with all the checkpoint inhibitors approved for treating multiple types of cancer, there are several cancer types for which there is a deep selection of checkpoint inhibitors available as a treatment option.

FIGURE **18**

THE GUT MICROBIOME: UNCOVERING NEW AVENUES FOR CANCER PREVENTION, EARLY DETECTION, AND TREATMENT



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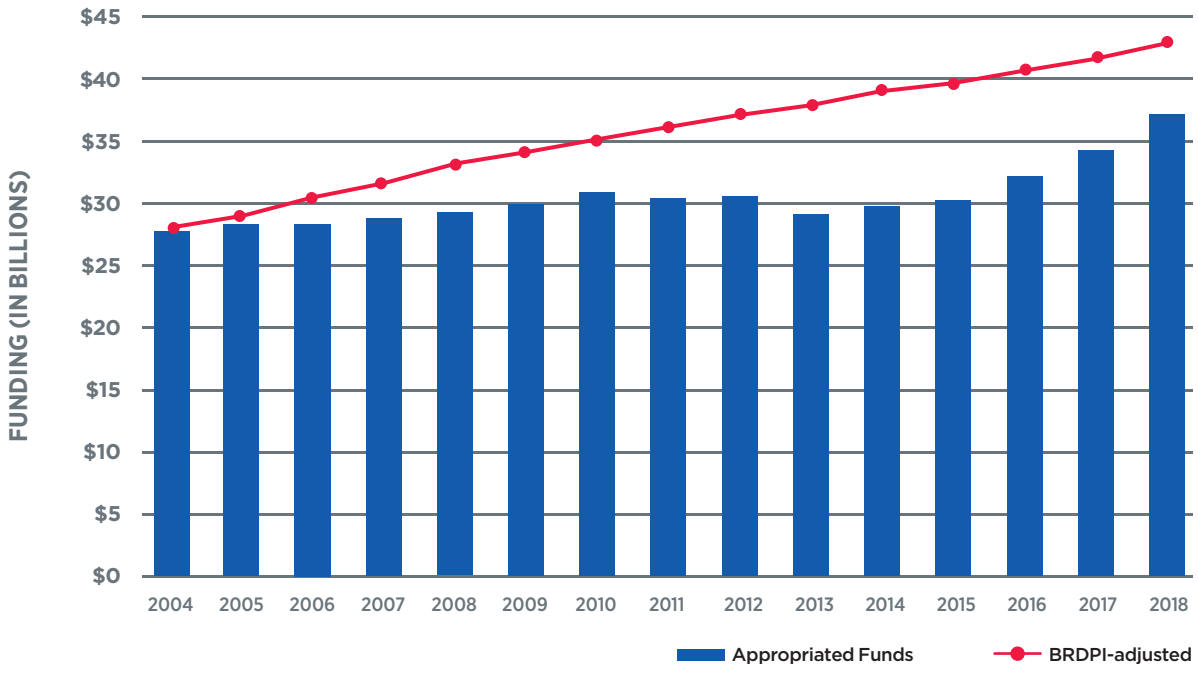
The gut microbiome is an exciting new area in cancer research. Investigations are under way to study whether it is possible to harness the human gut microbiome to prevent, detect, diagnose, or optimize cancer treatment. Manipulating the microbiome through lifestyle modifications such as changes in diet might aid in cancer prevention by suppressing chronic inflammation, while detection of certain microbial species that are frequently associated with cancer incidence may help in early detection or diagnosis of disease. The gut microbiome may also have a dramatic impact on the efficacy of anticancer immunotherapies and chemotherapies. Manipulating the microbiome in cancer patients through advanced probiotics, fecal transplantation, or pharmacologic interventions may open up new opportunities to improve patient outcomes and further precision medicine.

FIGURE **19**

NIH FUNDING: CLOSING THE GAP WITH THREE CONSECUTIVE YEARS OF ROBUST INCREASES



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 has received three consecutive years of significant funding increases, which have resulted in the first real budget growth in more than a decade and a 23 percent increase in funding since fiscal year 2015.

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