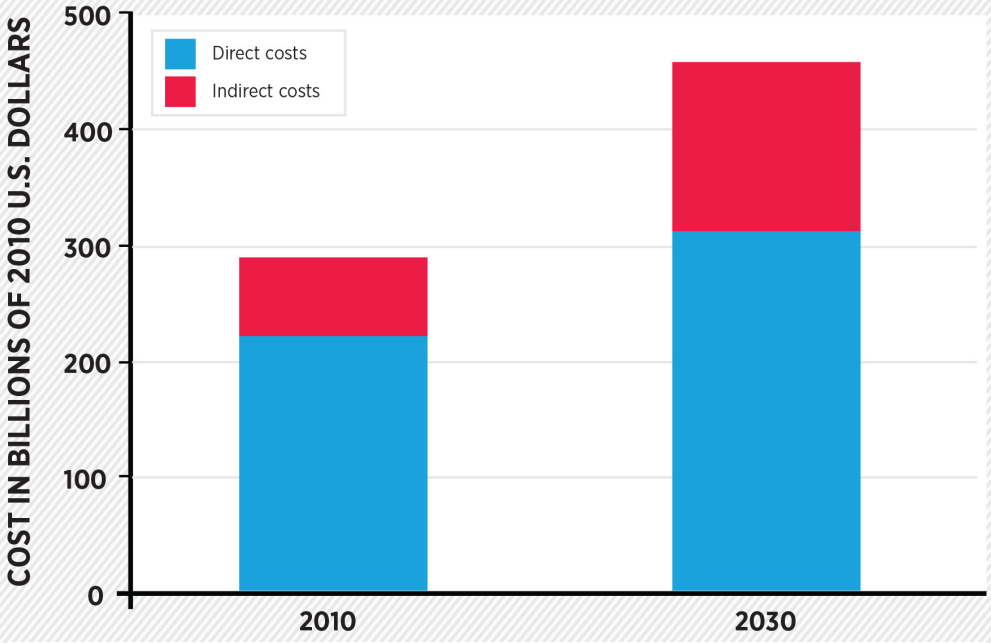
FIGURE 1

CANCER: A COSTLY DISEASE FOR THE WORLD



The global economic toll of cancer is enormous, and it is expected to balloon in the coming decades as the number of cancer cases rises, from 13.3 million cases in 2010 to an estimated 22 million in 2030. The costs of cancer can be separated into direct costs (blue bar) and indirect costs (red bar). Direct costs include the costs of medical procedures and services associated with treatment and care, as well as nonmedical costs, including caregiving expenses and the costs of transportation for treatment and care. Indirect costs are defined as income losses as a result of treatment or disability.

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FIGURE 2

WHAT IS 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. Through this approach, treatment of each patient can be focused on therapeutics most likely to yield benefit, sparing a patient the cost of and potential harms from those therapeutics that are unlikely to be of benefit. Factors such as a person's genome, the genome of his or her cancer, disease presentation, gender, exposures, lifestyle, microbiome, and other yet-to-be-discovered features (depicted as the question mark) are considered in precision medicine. Currently, genomics is the predominant factor influencing precision medicine in oncology, and oncology is leading the way in precision medicine. The order in which the factors appear is not meant to imply that one factor is more important than another.

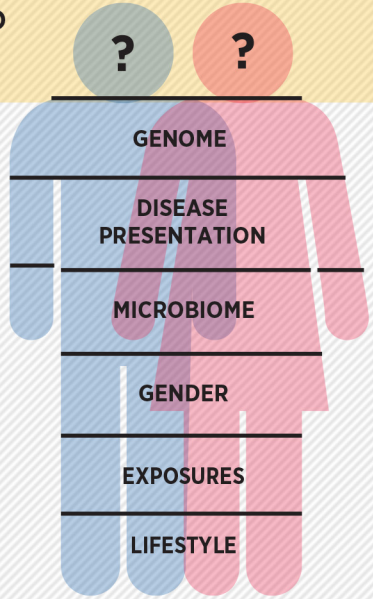

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FIGURE 3

THE INCREASING PRECISION OF ANTICANCER THERAPEUTICS

Research has powered the discovery and increased understanding of the factors most associated with cancer. As this knowledge has grown, our anticancer therapeutics have become more precisely targeted to those factors responsible for the development of the disease, meaning that less harm can occur to normal cells. The earliest categories of anticancer therapeutics target DNA, which is present in every cell of the body. Such therapeutics stop dividing cells, both cancerous and noncancerous, by inhibiting synthesis of or causing damage to DNA (dark blue circles). Recently, several new anticancer therapeutics have been approved that target not DNA directly, but rather the proteins that modify it (light blue circle), which can be altered in specific forms of hematopoietic malignancy, making them more disease-specific. Likewise, the understanding that estrogen, in addition to its normal role in endocrine function, also fuels the majority of breast cancers provides a more precise therapeutic target compared with stopping the synthesis of or causing damage to DNA (black circle). Angiogenesis, or the growth of new blood vessels from the existing vasculature, is essential to both normal physiology and cancer growth and metastasis. The identification of key molecules involved in this process has led to the development of 11 anticancer therapeutics that interrupt both normal and cancer-associated angiogenesis (red circle). Likewise, a deeper understanding of the normal function and regulation of the immune system has led to the development of numerous classes of therapeutics that modify the immune system (dark green circles) . The revolution in molecular biology identified many of the various proteins involved in the numerous cell-signaling networks that allow for normal cell function, some of which also play a role in cancer development and progression. With this knowledge came the ability to develop therapeutics called cell-signaling inhibitors that specifically block some of these proteins (gray oval). Moreover, the understanding that some of the genetic mutations that cause cancer lead to cancer-specific versions of cell-signaling proteins allowed for the development of our most precise therapeutics to date, leading to a range of disease precision within this category of anticancer therapeutics. Note: Only the major anticancer therapeutic categories are depicted.

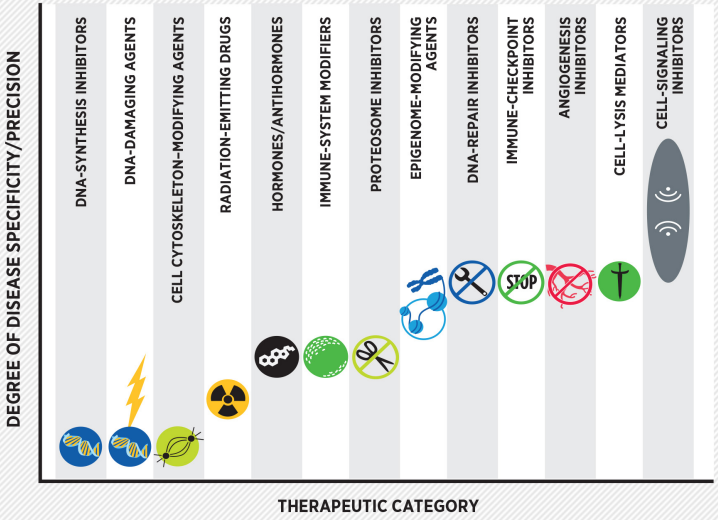

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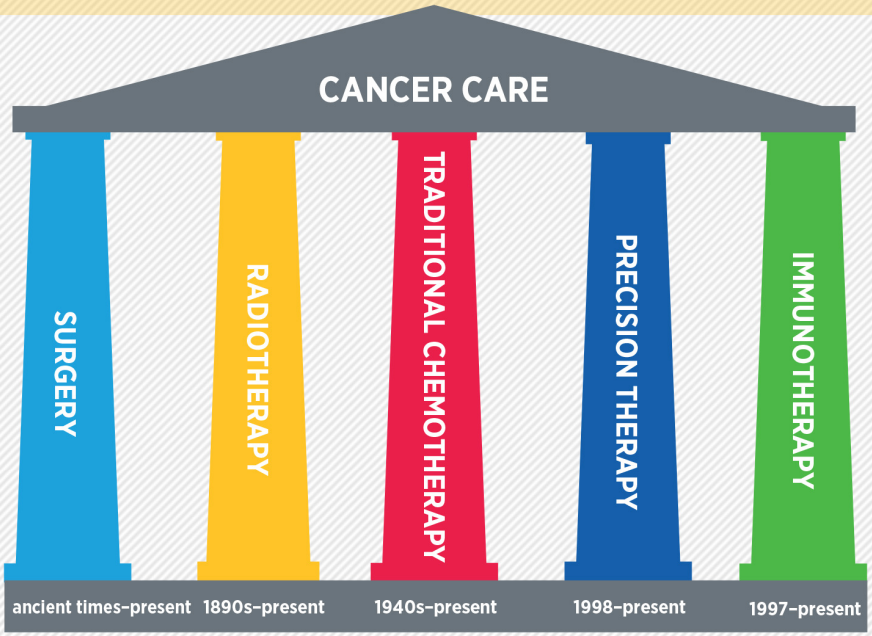
FIGURE 4

MORE OPTIONS FOR CANCER CARE



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, traditional chemotherapy, were laid in the early 1940s when a derivative of nitrogen mustard was explored as a treatment for lymphoma. These three pillars—surgery, radiotherapy, and traditional chemotherapy–continue to be mainstays of cancer care. 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 five years.

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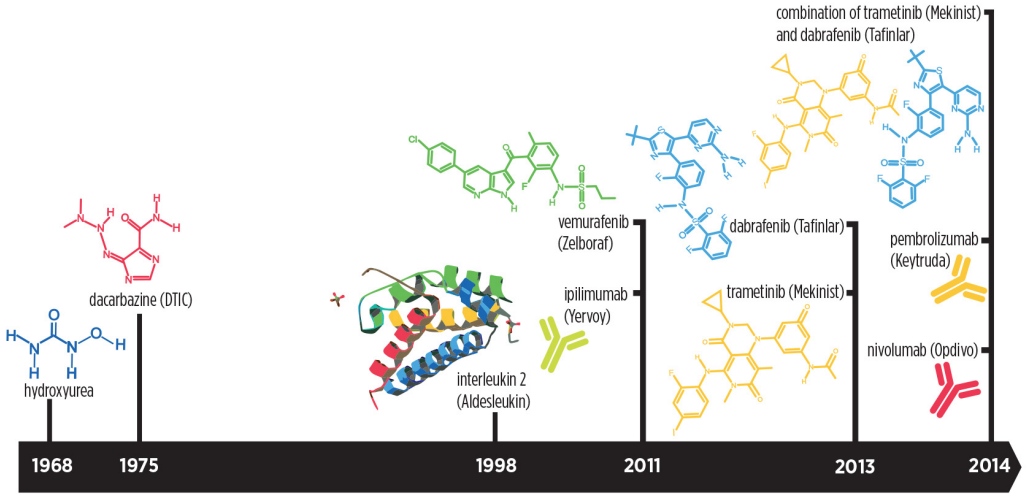
FIGURE 5

MAKING UP FOR LOST TIME



The DNA synthesis inhibitor hydroxyurea was the first FDA-approved therapeutic for the systemic treatment of metastatic melanoma. Its approval in 1968 was followed by the approval of the DNA-damaging agent dacarbazine (DITC) in 1975. Twenty-three years passed before another systemic therapeutic, the immune system stimulator recombinant interleukin 2 (Aldesleukin), was approved for the treatment of melanoma. In 2011, ipilimumab (Yervoy) became the first immune-checkpoint inhibitor approved by the FDA, and the first new systemic treatment for melanoma in 17 years. That year also saw the approval of vemurafenib (Zelboraf), a therapeutic that selectively inactivates the mutant form of the protein BRAF that occurs in approximately 50 percent of melanomas. In 2013, the FDA approved a second mutant BRAF–targeted agent, dabrafenib (Tafinlar), as well as a therapeutic that targets another protein in the BRAF signaling pathway, trametinib (Mekinist), for the treatment of BRAF-mutant metastatic melanoma. The combination of dabrafenib and trametinib was FDA approved for the treatment of BRAF-mutant metastatic melanoma in 2014. Finally, in 2014, the FDA approved two new immune-checkpoint inhibitors, nivolumab (Opdivo) and pembrolizumab (Keytruda). Note: This timeline focuses on systemic, primary treatments for regional and metastatic melanoma; other therapeutics have been approved for the prevention of disease recurrence or the treatment of localized lesions.

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FIGURE 6

HOW BIG IS BIG?

Data of any kind are measured in bytes. A byte is 8 binary digits (the 01011010 below) and is recognized by a computer as a single character. A thousand bytes make up a kilobyte (kB); the average Word document (paper) is tens to hundreds of kB. The average compact disc can hold 700,000 kB, which is 700 megabytes (MB), of data (gold disc). A thousand MB are contained within a gigabyte (GB), illustrated by the thumb drive, and the average digital video disc (DVD) holds nearly 5 GB of data (gold DVD). It would take more than 80 DVDs to store the data from sequencing an individual's entire genome (the circos plot), which is approximately 400 GB. A 2011 McKinsey/MGI report estimated that all of the world's recorded music up to that year could be stored in 6 terabytes (TB; G-clef); it would take 6,000 1-GB thumb drives to store all of these data. As of April 25, 2012, the Library of Congress' digital holdings collection contained 3 petabytes (PB; stack of books) of data, which is 3,000 terabytes or 3 million 1-GB thumb drives.

Researchers at the Lawrence Berkeley National Laboratory estimate that within the next few years, it will generate more than an exabyte (EB; cloud) of data modeling the weather. It would take more than 1 billion 1-GB thumb drives to store these data. It is estimated that in 2010, the world collectively created more than 1.2 zetabytes (ZB; globe) of data. Big data sets are unique in that they are too large to be stored and analyzed using traditional relational methodologies. The complexity of cancer and its treatment is creating big data sets, and the field and the patients it serves will benefit greatly from research into big data systems, methodologies, and solutions.

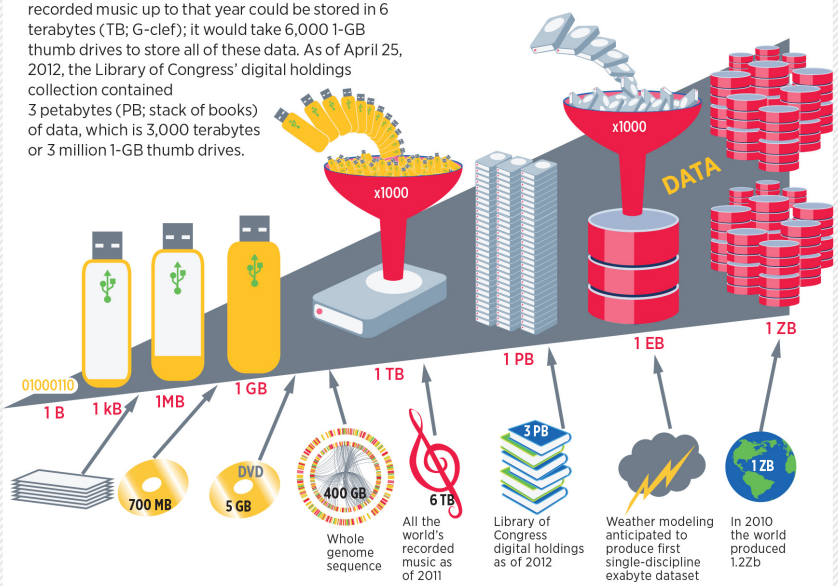

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FIGURE 7

GENOMICALLY INFORMED CLINICAL TRIALS

One of the major uses of genomics in clinical research is in the design and execution of novel 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 8

RISKY BUSINESS

Research has identified numerous factors that increase an individual's risk for developing cancer. Not all factors have the same impact on cancer risk. The factors that have the biggest impact are tobacco use, obesity and overweight, infection with one of several microorganisms, poor dietary habits, and lack of physical activity. By modifying their behaviors, individuals can eliminate or reduce many of these risks, and therefore reduce their risk of cancer. Moreover, more effective public education and policy initiatives could help further reduce the burden of cancers related to modifiable risk factors.

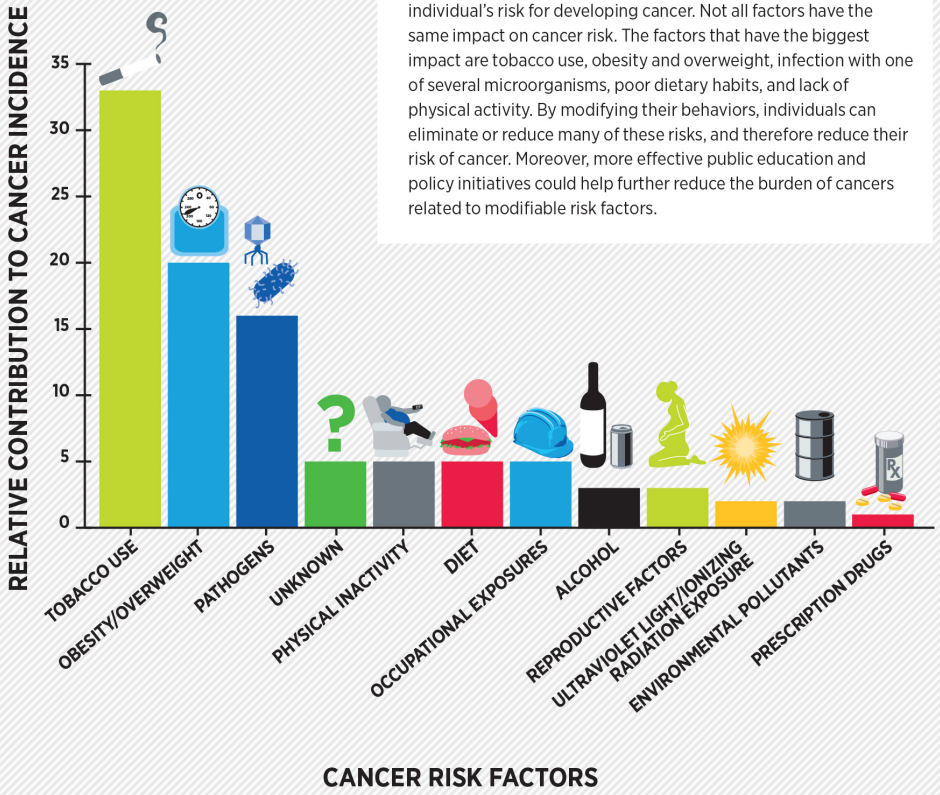

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FIGURE 9

CLEARING THE AIR

Since the link between cigarette smoking and cancer was first brought to the public's attention in 1964, numerous policies have been enacted to reduce the exposure of both smokers and nonsmokers to cigarette smoke. In addition, many of these policies were also designed to reduce smoking prevalence, particularly by discouraging youth from beginning smoking. The policies largely fall into five different categories: increased taxes; increased education; public warnings; elimination of exposure to cigarette smoke in public places; and reduced exposure to cigarette advertising. In 2009, the Family Smoking Prevention and Control Act gave the U.S. Food and Drug Administration (FDA) direct authority to regulate the manufacture, distribution, and marketing of tobacco products. As a result, cigarettes are now subject to public health–based regulation.

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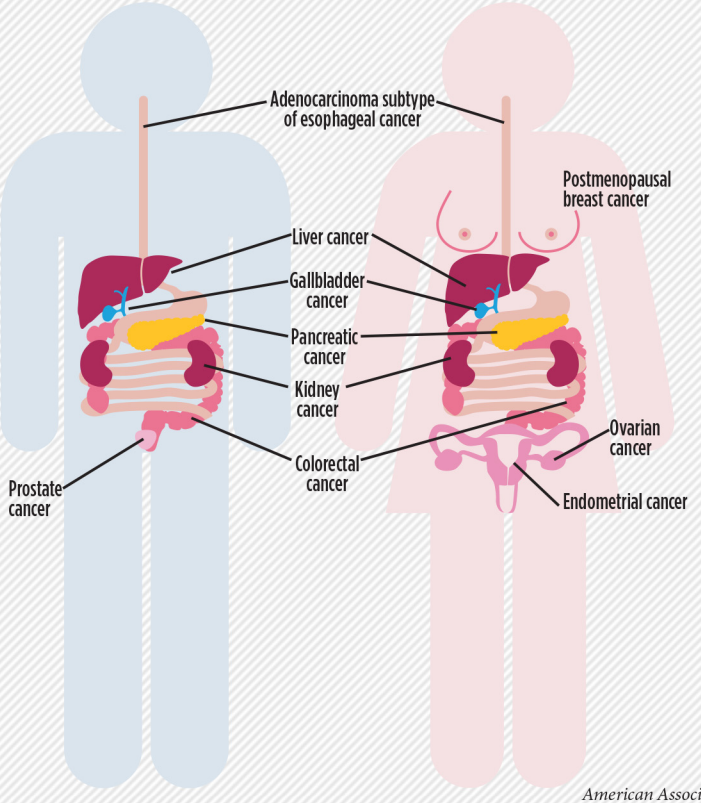
FIGURE 10

WEIGHING THE EVIDENCE: CANCERS CAUSED BY OBESITY



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

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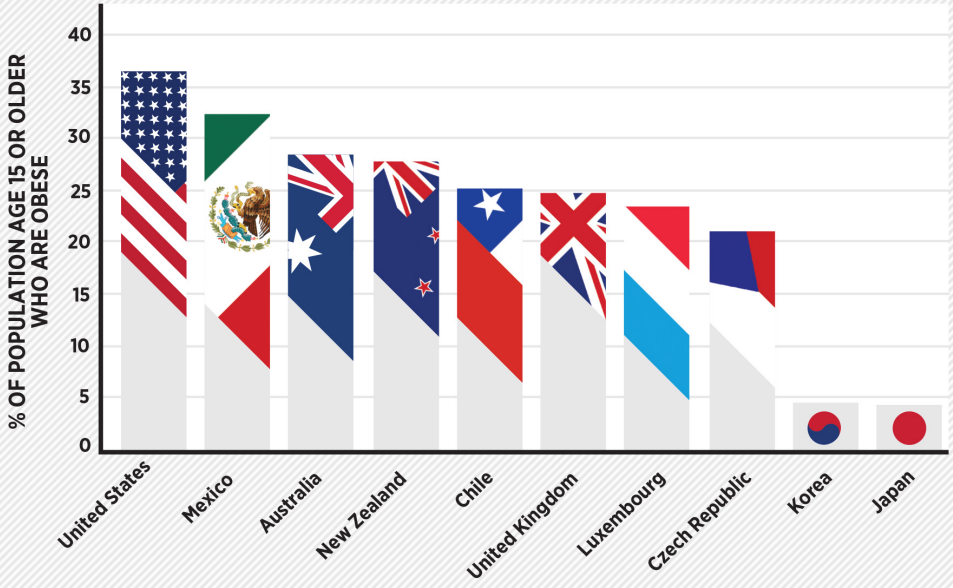
FIGURE 11

A HEAVY ISSUE



Among the 34 Organization for Economic Cooperation and Development (OECD) countries, the United States has the highest prevalence of obesity in the segment of its population age 15 or older. Depicted here are the 10 OECD countries for which data on obesity are based on actual measurements of height and weight data. The data are from 2011 with the exception of the United States (2010), Mexico (2012), New Zealand (2009), Chile (2009), and the Czech Republic (2010). Among the countries for which only self-reported data are available, 20 percent or more of the population age 15 or older was obese in Iceland (2010 data) and Hungary (2009 data), taking to 10 the number of OECD countries where at least one in every five people age 15 or older is obese. Note: Only countries for which measured data are available are shown.

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FIGURE 12

CATCHING A CAUSE OF CANCER

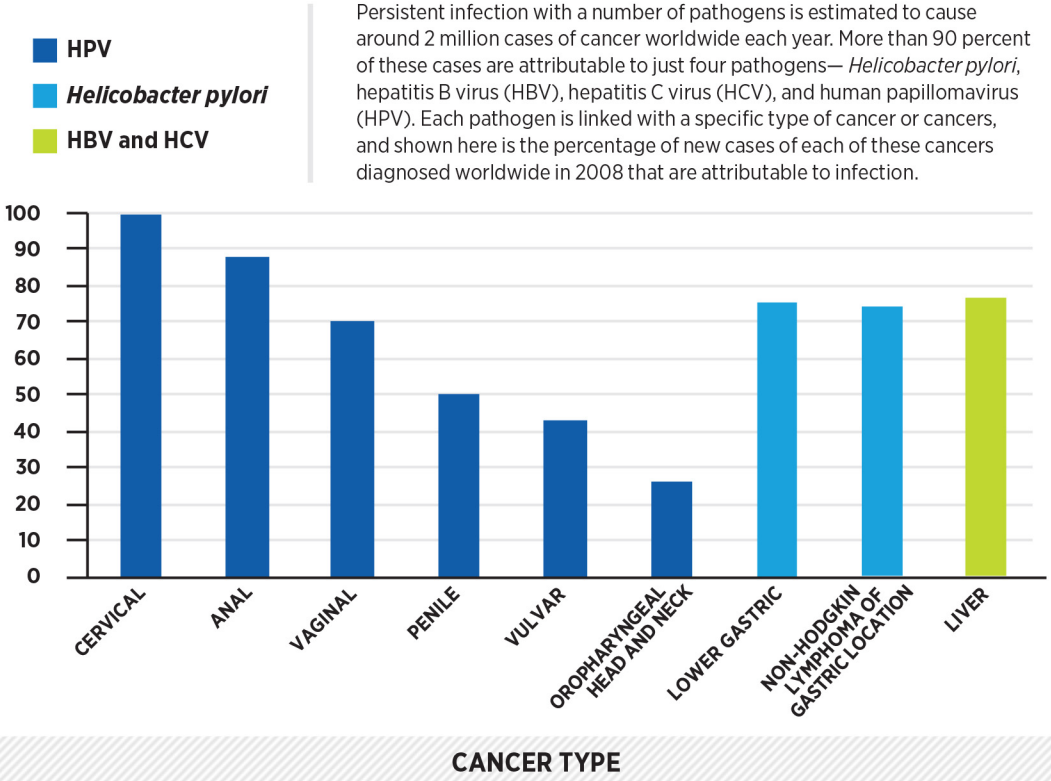

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FIGURE 13

PRECISION PREVENTION

Precision prevention is a conceptual framework that aims to tailor cancer prevention to the individual patient by accounting for the various factors that may play a role in developing a particular cancer; it is analogous to the manner in which precision medicine treats patients. Among the various factors that could be considered in the implementation of precision prevention are: age; gender; family history, including genetic predisposition to developing cancer; lifestyle factors including tobacco and alcohol use, being overweight or obese, and levels of exercise; reproductive and medical factors; exposures to known carcinogens like viruses; socioeconomic status; and geography, as well as yet-to-be identified factors, as indicated by the question mark. The order in which the factors appear is not meant to imply that one factor is more important than another.

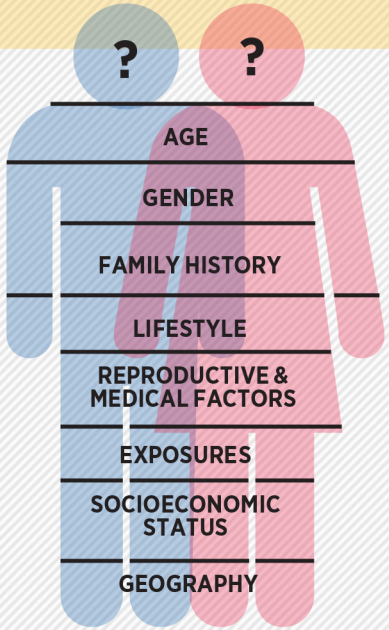

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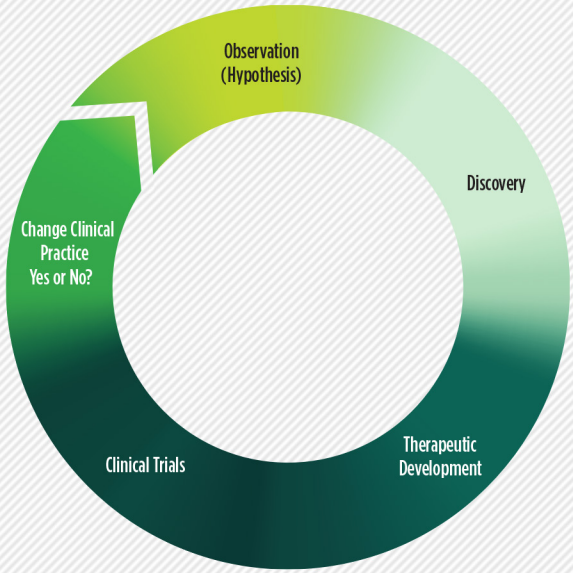
FIGURE 14

THE BIOMEDICAL RESEARCH CYCLE



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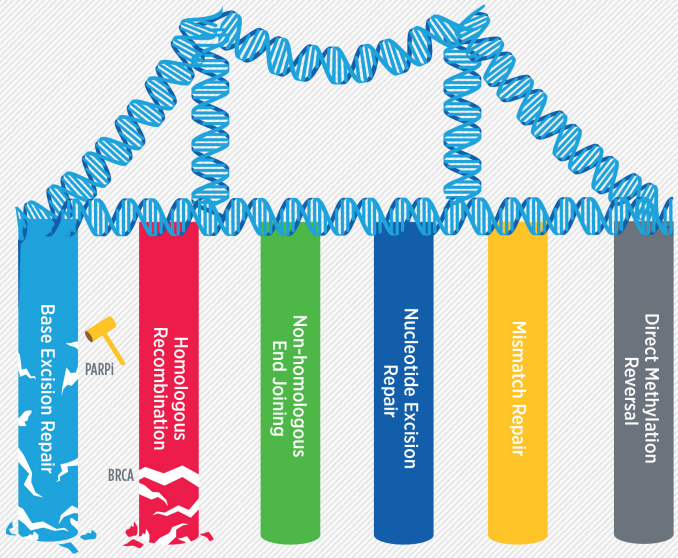
Results from any type of research can fuel the biomedical research cycle by providing observations relevant to the practice of medicine, leading to questions, or hypotheses, that are tested in experiments during the discovery phase of research. During the discovery phase, traits unique to a disease may 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 15

DNA INTEGRITY: BRIDGING THE PRECISION GAP



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 toxins 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, and if too many mutations are present, a cell will die. 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 treating ovarian cancer patients who inherited a defective BRCA1 or BRCA2 gene with the PARP inhibitor olaparib (Lynparza; yellow hammer) can lead to pervasive DNA damage, resulting in the death of the cancer cells.

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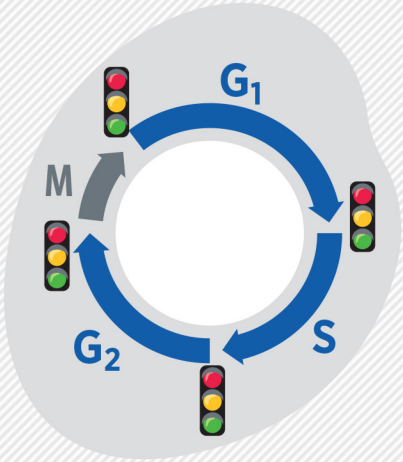
FIGURE 16

CHECKING CELL MULTIPLICATION



Palbociclib (Ibrance) exerts its anticancer effects by blocking the function of two proteins that play a role in driving cell multiplication—cyclin-dependent kinase 4 (CDK4) and CDK6. 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 (G_1, S, G_2, and M). CDK4 and CDK6 promote passage through the checkpoint between the G1 and S phases of the cell cycle. Thus, blocking these proteins with palbociclib can prevent cell multiplication.

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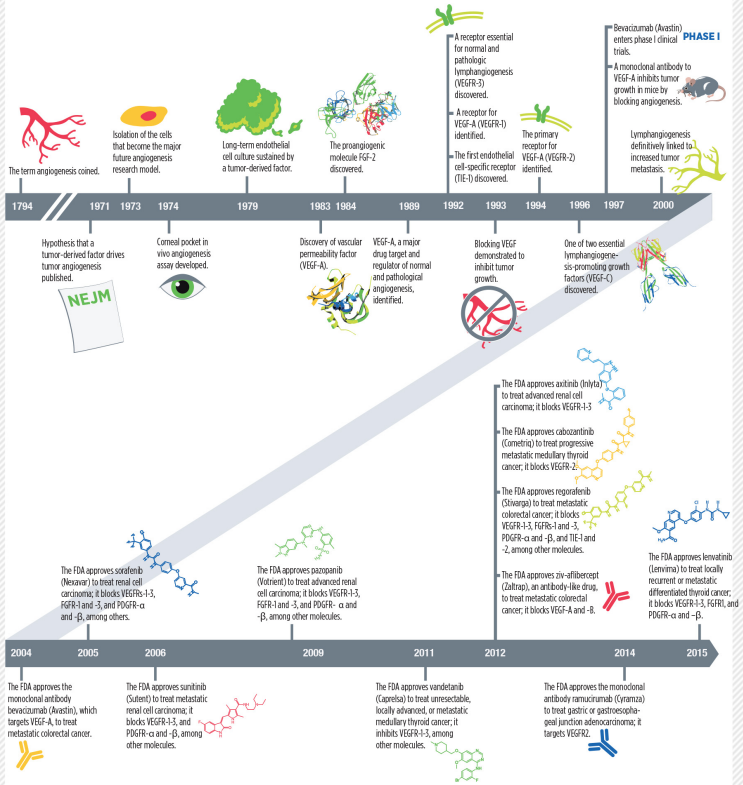
FIGURE 17

BRANCHING OUT: A NEW ANTIANGIOGENIC THERAPEUTIC



In the past 11 years, the U.S. Food and Drug Administration (FDA) has approved 11 anticancer therapeutics that work by blocking the development of new blood vessels (angiogenesis). Bevacizumab (Avastin) was the first of these drugs, which are known as antiangiogenic agents, to be approved, in 2004, and lenvatinib (Lenvima) the most recent, in 2015. Research into the processes of angiogenesis and lymphangiogenesis, in both normal and pathological conditions, including cancer, helped identify many of the molecular regulators of these processes, and these regulators are the specific targets of the 11 antiangiogenic agents. The first date of approval for each of these therapeutics is indicated on the timeline; however, most of these agents received approval from the FDA for the treatment of additional cancers in subsequent years, including bevacizumab, which was approved for the treatment of persistent, recurrent, or metastatic cervical cancer and platinum-resistant recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer in 2014.

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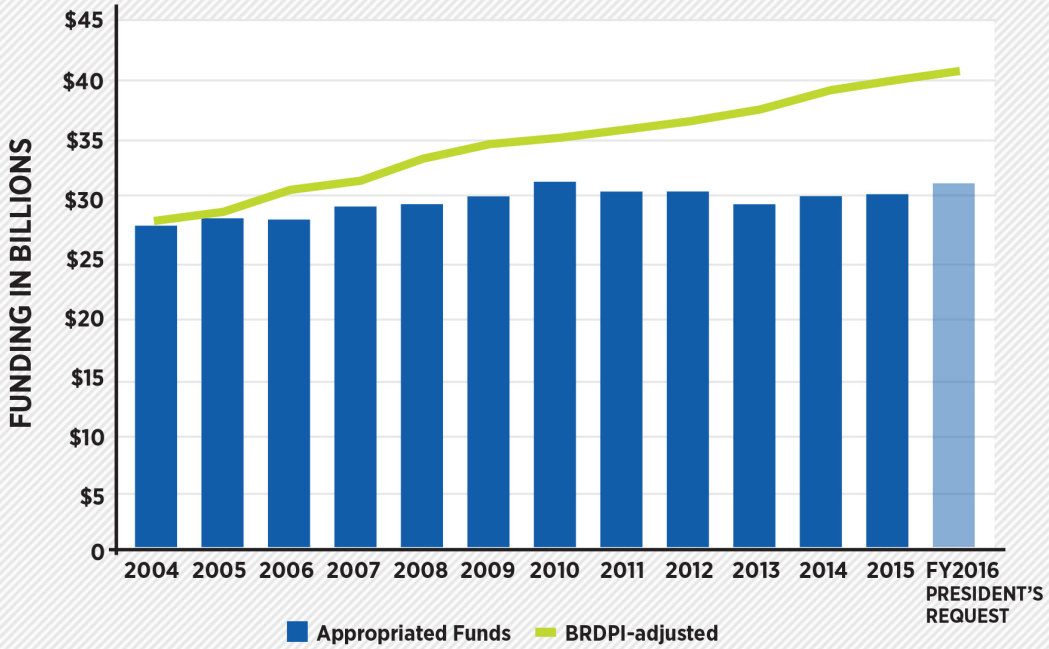
FIGURE 18

FALLING BEHIND

The Biomedical Research and Development Price Index (BRDPI) reflects the rising cost of personnel, supplies, and equipment needed to conduct biomedical research. Since 2004, the National Institutes of Health (NIH) budget has not kept pace with BRDPI. As a result, the NIH has lost approximately 25 percent of its ability to fund lifesaving research.



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