



## Aiming High — Changing the Trajectory for Cancer

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**“F**or the loved ones we’ve all lost, for the families that we can still save, let’s make America the country that cures cancer once and for all” (President Barack Obama, State of the Union Address, January 12, 2016).

*“We’re talking about prevention and early detection. I’m convinced we can get answers and come up with game-changing treatments and get them to people who need them. We have an opportunity to fundamentally change the trajectory”* (Vice President Joe Biden, University of Pennsylvania Abramson Cancer Center, January 15, 2016).

Cancer is hundreds of diseases. Biomedical research has made it possible to cure some of them, including most cases of childhood leukemia and Hodgkin’s lymphoma, and has spurred significant progress in treating others. Indeed, over the past quarter century, U.S. cancer mortality rates have decreased by 23%, as medicine has saved an estimated 1.7 million lives and prevented immeasurable

suffering. Much of this success has been fueled by strong, sustained federal investments in basic, epidemiologic, and clinical research and resulting advances in prevention, screening, diagnosis, and therapy. Yet more progress is urgently needed. Cancer is the second-leading cause of death in the United States and is expected to kill nearly 600,000 Americans in 2016 — about 1600 people every day.

President Obama’s call for a new initiative, led by Vice President Biden, to galvanize research efforts against cancer, is not the first sweeping anticancer campaign ever proposed — indeed, President Richard Nixon unveiled a “War on Cancer” in 1971. So questions have arisen about why

such an initiative is needed now and what’s different today from 45 years ago.

We believe the time is right for a renewed surge against cancer because, thanks to the coalescence of new scientific insights and technological innovations, prospects for success are greater than ever. One instrumental advance has been a dramatic shift in our fundamental understanding of cancer. Work using tools and technologies arising from the Human Genome Project and data from the Cancer Genome Atlas and other studies has clarified that cancer is a disease of the genome. It has become increasingly apparent that knowing what driver mutations are present in a particular tumor is often more important than knowing which organ system it arose from. Genomic technology has also shown that although each tumor is molecularly unique, certain pathways are repeatedly affected — findings that have

informed the design and use of a new generation of drugs targeting those pathways.

Another rapidly evolving area of inquiry looks beyond tumor cells to other factors, such as stromal and immune cells in the tumor microenvironment that often affect tumor progression. Powerful new bioinformatics tools and methods enable assembly, management, and analysis of very large sets of complex molecular and clinical data, or “big data,”

to apply and build on all the recent advances in our understanding of cancer biology and new therapeutic approaches while also making progress in prevention, screening, and early detection. The new cancer-research initiative aims to make a difference in all these areas by addressing two overarching priorities: increasing the resources devoted to fighting cancer and breaking down silos to unite the cancer-fighting community. Coordination throughout

nology, single-cell genomic analysis, immunotherapy, a focus on pediatric cancer, and enhanced data sharing (see table).

The panel will tap into the expertise of scientists, oncologists, patient advocates, philanthropists, and representatives of the pharmaceutical and biotech industries to focus on emerging frontiers in the understanding and treatment of cancers. New opportunities for collaboration among government agencies and between the public and private sectors are being explored and will be highlighted at a summit in the late spring. We expect these discussions to uncover meritorious and previously unanticipated scientific opportunities to reduce cancer incidence and improve real-world cancer outcomes, including opportunities that seek to narrow or overcome disparities in cancer prevention, screening, and treatment that affect rural, poor, and minority populations.

To maximize the scientific community's ability to take advantage of these emerging possibilities, the blue-ribbon panel will explore the possibility of establishing an Exceptional Opportunities in Cancer Research Fund to support the pursuit of new ideas addressing currently intractable problems in cancer research. The National Cancer Institute (NCI) could then respond quickly to leverage novel insights in any area of oncology that's ripe for expansion — from basic science through translational approaches to clinical trials. Such an investment would help to ensure that our country's most creative scientists have the necessary resources to pursue investigations that may lead to breakthroughs.

A second goal of the initiative

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which are necessary for generating predictive models of cancer progression and therapeutic response.

Meanwhile, after a decades-long struggle, strategies for spurring the immune system to attack cancer cells have begun to achieve dramatic successes. Some such immunotherapies, including checkpoint inhibitors and chimeric antigen receptor T-cell therapies, have been shown to induce remissions or even cures in people with treatment-resistant forms of melanoma, leukemia, and lymphoma, as well as late-stage mesothelioma and ovarian, lung, kidney, and triple-negative breast cancers. However, many solid tumors fail to respond well to these approaches, and initially positive responses are not always sustained. There is still much work to do.

Clearly, it will be a monumental challenge to figure out how

the government is being enhanced by a high-level Cancer Moonshot Task Force involving multiple departments and led by the Vice President.<sup>1</sup>

Fueled by an additional \$680 million in the proposed fiscal year 2017 budget for the National Institutes of Health (NIH), plus additional resources for the Food and Drug Administration, the initiative will aim to accelerate progress toward the next generation of interventions that we hope will substantially reduce cancer incidence and dramatically improve patient outcomes. The NIH's most compelling opportunities for progress will be set forth by late summer 2016 in a research plan informed by the deliberations of a blue-ribbon panel of experts, which will provide scientific input to the National Cancer Advisory Board.<sup>2</sup> Some possible opportunities include vaccine development, early-detection tech-

| Potential Opportunities for Cancer Research, Fiscal Year 2017. |  |   |
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| Potential Research Area  | Scientific Rationale   | Possible Activities   |
| Cancer vaccines  | Cancers caused by viruses or cancers that produce unique or signature premalignant genetic changes may be preventable by vaccines.   | Produce Epstein–Barr virus (EBV) vaccine for human-safety testing; explore development of other vaccines for high-risk persons.   |
| Early cancer detection   | Tumors shed DNA, RNA, exosomes, and other biologic materials into the circulation and into other fluids, where they can be detected.   | Develop tools and techniques to improve sensitivity, specificity, and utility of molecular-detection assays.  |
| Single-cell genomic analysis                                   | Genomic mutations that occur in tumor cells and nearby cells (stromal, immune) can inform the design of drugs and immunotherapy.   | Conduct single-cell analyses to uncover the -omic spectrum of malignant and nonmalignant cells in the tumor microenvironment.   |
| Cancer immunotherapy   | Key molecules on cancer cells may make them more (or less) likely to attract tumor-killing immune cells.   | Support basic research to further elucidate cancer immunology and extend the reach of immunotherapy to all kinds of cancer.   |
| Pediatric cancer   | In contrast to adult cancers, many childhood tumors are driven by transcription factors that are permanently switched on, which has made it more difficult to develop drugs to treat them. | Prepare and screen new libraries of compounds chosen for their potential to interfere with these transcription factors; intensify the collection and analysis of very rare childhood cancers. |
| Data sharing   | Sharing data can break down barriers between institutions and maximize the benefits of this knowledge for patients.  | Expand capacity of the National Cancer Institute Genomic Data Commons to handle and analyze genomic and clinical data from patients and health care providers.                                |
| Exceptional Opportunities in Cancer Research Fund              | Providing competitive opportunities for high-risk, high-reward ideas can stimulate innovation.   | Pursue previously unanticipated and novel scientific opportunities to improve basic and applied cancer research.  |

will be to overcome barriers that often prevent collaboration and information sharing among the various groups working to defeat cancer and that limit access to state-of-the-art research.<sup>3</sup> With leadership from the Cancer Moonshot Task Force, efforts to align the endeavors of government, industry, academia, philanthropy, and patient groups will be amplified. In addition, data and technology innovators will help to revolutionize the ways in which cancer-related data are shared and used to achieve new breakthroughs, and the federal government may seek ways to facilitate data sharing among researchers

 **An audio interview with Greg Simon is available at [NEJM.org](http://NEJM.org)**

who are currently reluctant to disseminate their data and results. The NCI's Cancer Genomic Data Commons and Cancer Genomics Cloud Pilots are both examining new methods to facili-

tate sharing of data, novel algorithms, software, tools, and annotations, and they provide ways of measuring the impact of such sharing.

Vice President Biden has also made it clear that he wants to take steps to ensure that all Americans — even those who have limited resources or live far from major cancer centers — have access to leading-edge cancer treatment, prevention, and screening approaches. Currently, less than 5% of U.S. adults with cancer take part in clinical trials.<sup>4</sup> In addition, community oncologists, who currently treat about two thirds of patients with cancer,<sup>5</sup> often have limited access to new research and related advances and face potential financial disincentives to enrolling their patients in trials. Following a participant-centric model being pioneered in the NIH-led Precision Medicine Ini-

tiative, the cancer-research effort will be informed by input from the patient community and will ensure that patients and their families are treated as partners, with access to their own health information and opportunities to contribute to research.

Although key actions and deliverables remain a work in progress, one aim of this new initiative is certain: to inspire a new generation of American visionaries to defy the boundaries of current knowledge about cancer. Unleashing the talents of the scientific community by providing a strong, steady stream of resources should enable biomedical research to accelerate progress in the fight against cancer. We expect these efforts to build a firm foundation for the development of better means of prevention, treatment, and cure for all types of cancer.

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## Essential Medicines in the United States — Why Access Is Diminishing

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On August 10, 2015, Turing Pharmaceuticals bought the marketing rights to pyrimethamine (Daraprim), a decades-old first-line treatment for toxoplasmosis. The price of pyrimethamine immediately increased by 5433%. Heavy scrutiny followed, and although Turing agreed to reduce the price, the drug remains prohibitively expensive for many patients. Recently, at our hospital, an immigrant patient with a new diagnosis of HIV–AIDS and toxoplasmosis couldn't receive first-line therapy because of cost: the price for 100 pills was \$75,000. The patient is currently receiving second-line therapy.

Unfortunately, the highly publicized pyrimethamine acquisition is not unique. Prices have been quietly but dramatically increasing for many older, off-patent drugs. Some of these medicines are considered essential by the World Health Organization (WHO) (see Table 1). In some cases, price hikes have disproportionately affected vulnerable populations, making potentially life-saving therapies unavailable to

disadvantaged patients. It seems that a new business model has emerged: companies are acquiring drugs in niche markets where there are few or no therapeutic alternatives in order to maximize their profits. Unlike new brand-name drugs, the patents of the drugs being targeted by this model expired years ago. These companies seem to have no interest in adding value to the health care system by developing new drugs.

The increased cost of albendazole, an antiparasitic medication, is a case in point.<sup>1</sup> CorePharma acquired the U.S. marketing license for albendazole from GlaxoSmithKline in 2010 and subsequently sold it to a private equity group, Amedra Pharmaceuticals. Amedra then bought the only potential competitor available on the U.S. market, mebendazole, from Teva Pharmaceuticals. Since Amedra's acquisition, albendazole's average wholesale price has increased by 3299%, from \$5.92 per typical daily dose in 2010 to \$201.27 in 2015.<sup>2</sup>

Other pharmaceutical compa-

nies have also used this strategy for manipulating the market. Valeant Pharmaceuticals, a publicly traded company with 2014 revenues of \$8.25 billion, has taken a similar approach with several drugs. Valeant has been forthright about its goal of maximizing profits for shareholders while minimizing research-and-development (R&D) costs; the company currently spends 3% of its total revenue on R&D. Rodelis Therapeutics, a private company with little public transparency, also became notorious for buying the rights to cycloserine — a niche medication used in multidrug-resistant tuberculosis — and immediately increasing its price by more than 2000%. In response to a negative public reaction, Rodelis has since sold the drug back to its previous owner.

Many factors contribute to high pharmaceutical prices, including drug shortages, supply disruptions, manufacturer consolidations, and R&D costs. Though some companies that have purchased and increased the price of niche medicines cite R&D as an