The White House Launches a Cancer Moonshot

Despite Funding Questions, the Progress Appears Promising

Stephen Barlas

Early in January 2016, the Obama administration, with great fanfare, announced a new initiative to find cancer cures. Vice President Joseph Biden was apparently the leading advocate for the effort. He wanted to honor his son Beau, who died from brain cancer in 2015. With an abundance of excitement and public relations strategy, Biden labeled the effort a "moonshot" and said he hoped to spur a decade's worth of advances in cancer research in five years.

But when Biden visited the Abramson Cancer Center in Philadelphia later in January, he was already backing away from the atmospheric moniker. The center's director, Chi Van Dang, PhD, MD, described a conversation in which the vice president said the choice of the term "moonshot" was unfortunate. Dr. Dang relayed the context of Biden's comment: "It implies something too simple; that we can just assemble the engineers and the astronauts, make the rocket, and we'll get to the moon and back."

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Maybe a better metaphor (drawn from the golf world) would have been "chip shot." Considerable progress has been made in the past decade in reducing cancer mortality rates, and the arrival of immunotherapies is giving victims of some cancers leases on life that were unfathomable just two years ago. Like golfers, health researchers are getting close to "the pin." But the terrain is tricky and there's no guarantee the ball will drop into the symbolic cup.

Richard Schilsky, MD, Chief Medical Officer of the American Society of Clinical Oncology (ASCO), put it this way:

> If there is anything that we have learned it is that there are hundreds of cancers and it is hard to make a sweeping statement. We are making remarkable progress in some cancers, like melanoma. Look at former President Jimmy Carter. A decade ago, he would have died from advanced melanoma. Now with Keytruda [pembrolizumab, Merck Oncology], he is cancer free. However, some cancers such as pancreatic are still very difficult to treat.

Whether it's described as a moonshot, a chip shot, or something else, Dr. Schilsky believes Biden has elevated the discussion about the need for a robust national commitment to cancer research. "He is taking it upon himself to break down silos in the cancer community," Dr. Schilsky states. "We don't have to go to the moon, we've already been there. But the vision needs to be transformative, in the same way the moonshot transformed our psyche."

Funding Uncertainty

Transformative visions are good, of course, but research is still the bedrock of cancer treatment developments, and it costs money—lots of it. To the extent that the Obama administration's cancer initiative has been criticized, it has been over its $1 billion budget. That figure consists of $775 million for cancer-related research requested for the 2017 fiscal year, which begins on October 1, 2016, and about $195 million for the National Institutes of Health (NIH) for the current 2016 fiscal year.[1]

Actually, many in the cancer community are unhappy with the way the White House has structured this $1 billion "moonshot" funding. First of all, the $195 million in fiscal 2016 will come from a rejuggling of existing National Cancer Institute (NCI) funds. There will be no new money. The $775 million in new spending in fiscal 2017 would come from a confusing maneuver in which the NIH budget would receive a $1.8 billion *mandatory* increase as part of its *authorization* while suffering a $1 billion decrease in its annual *appropriation*. That would yield the $800 million increase, and since it would be mandatory, that increase would be tacked on to NIH budgets, as protected funding, in future years. Of that $800 million extra, $680 million would go for the cancer "moonshot" initiative; $100 million for the "Precision Medicine Initiative Cohort Program," which was initially funded in the current 2016 fiscal year; and $45 million for "Brain Research through Advancing Innovative Neurotechnologies."

Congress has added to the budgetary confusion. The House has approved $1.8 billion in mandatory *additional* funds for the NIH in each of fiscal years 2017 to 2021 as part of the 21st Century Cures bill (H.R. 6) that it passed in July 2015 by a vote of 344–77.[2] So it essentially adopted the White House approach, which is problematic, in the eyes of the biomedical research community, because it would lead to three favored cancer-related programs getting increases and the remainder of the $32 billion or so in NIH programs (in fiscal 2016) having flat funding.

That opposition and other concerns about H.R. 6 have swayed the Senate, which appears unlikely to follow the House's lead. The American Association for Cancer Research (AACR) and cancer research advocacy groups don't support mandatory funding, and they aren't thrilled that the Obama administration proposed it. They prefer a $2 billion increase in the congressional appropriation for fiscal 2017 (not a *mandatory authorization*), which Republican leaders of the House and Senate Appropriations Committees seem to favor. Jon Retzlaff, Managing Director of Science Policy, Government Affairs, and Advocacy for the AACR, says, "We much prefer NIH growing at a robust, sustainable, predictable rate through the annual appropriation process. Roy Blunt and Tom Cole,

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the two Republican chairmen of the relevant appropriations subcommittees, have indicated they will support another significant increase for the NIH in 2017. We applaud that. We don't oppose mandatory spending, we oppose it supplanting increased appropriations." Congress did increase the NIH appropriation by $2 billion in fiscal 2016.

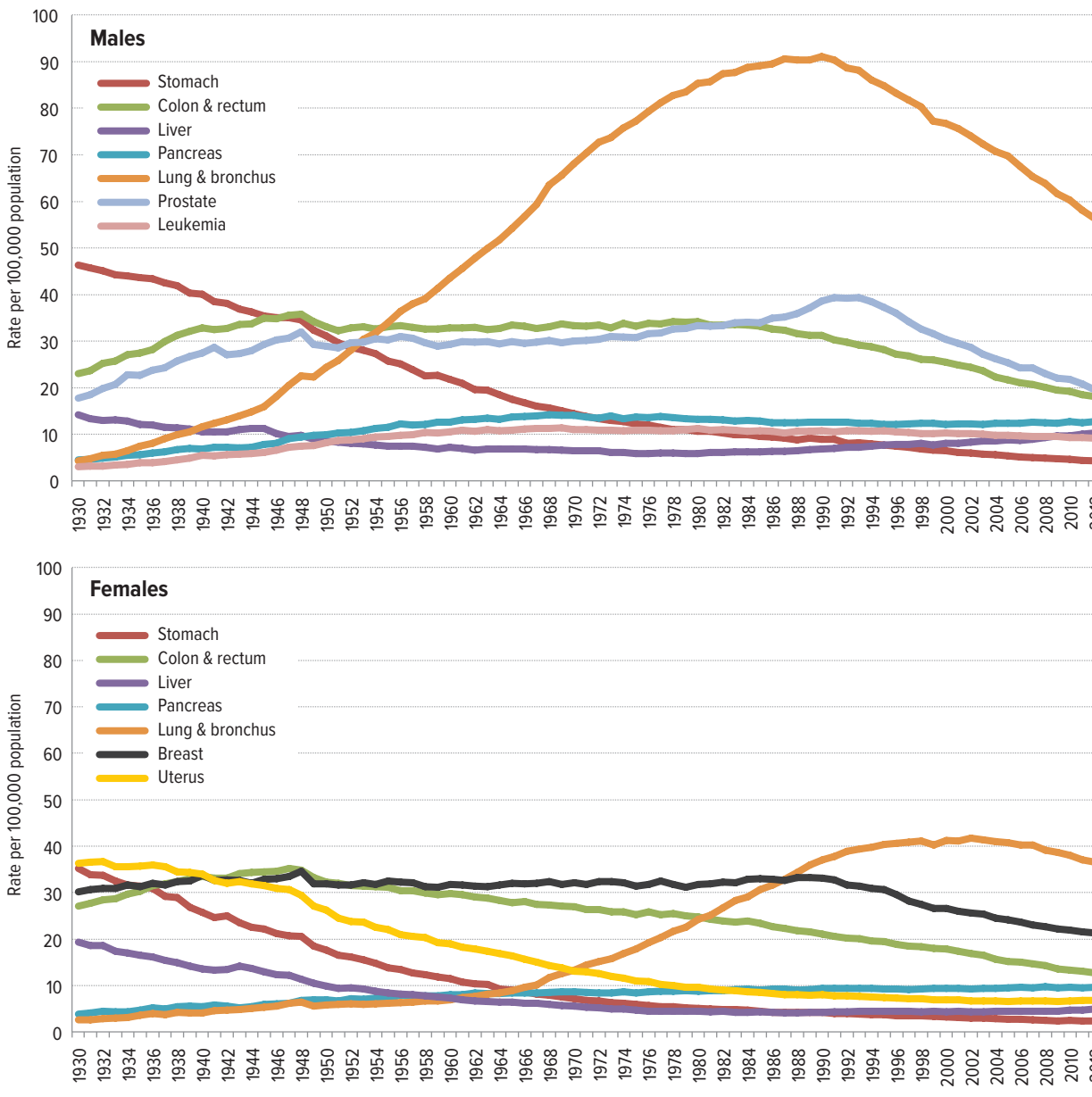
However, if Congress does decide to increase the NIH appropriation by $2 billion or some other sum in fiscal 2017, there is no guarantee that the White House moonshot will be funded in full. "Congress has historically sought to provide all the NIH institutes and centers with an increase when there's an overall increase in NIH funding," Retzlaff explains. "Therefore, Congress is likely to propose allocating the dollars differently than the President has proposed."

What's the Problem?

Of course, whatever additional funds the federal government commits to cancer research will be a drop in the bucket compared with what private industry spends. In May 2015, the IMS Institute for Healthcare Informatics reported total global spending on oncology medicines—including therapeutic treatments and supportive care—reached the $100 billion threshold in 2014,

Figure 1 Trends in Age-Adjusted Cancer Death Rates by Gender and Site, U.S., 1930–2012[4]

Rates per 100,000, age-adjusted to the 2000 U.S. standard population



Source: American Cancer Society, *Cancer Facts & Figures 2016*. Based on data from the National Center for Health Statistics, Centers for Disease Control and Prevention.

an increase of 10.3% over the year before, even as the share of total medicine spending on oncologics increased only modestly.[3] Growth in global spending on cancer drugs—measured using ex-manufacturer prices, which approximate the actual prices received by manufacturers and do not reflect off-invoice discounts, rebates, or patient access programs—increased at a compound annual growth rate of 6.5% on a constant-dollar basis during the past five years. Murray Aitken, IMS Health Senior Vice President and Executive Director of the IMS Institute for Healthcare Informatics, explains the trend:

> The increased prevalence of most cancers, earlier treatment initiation, new medicines, and improved outcomes are all contributing to the greater demand for oncology therapeutics around the world. Innovative therapeutic classes, combination therapies, and the use of biomarkers will change the landscape over the next several years, holding out the promise of substantial improvements in survival with lower toxicity for cancer patients.

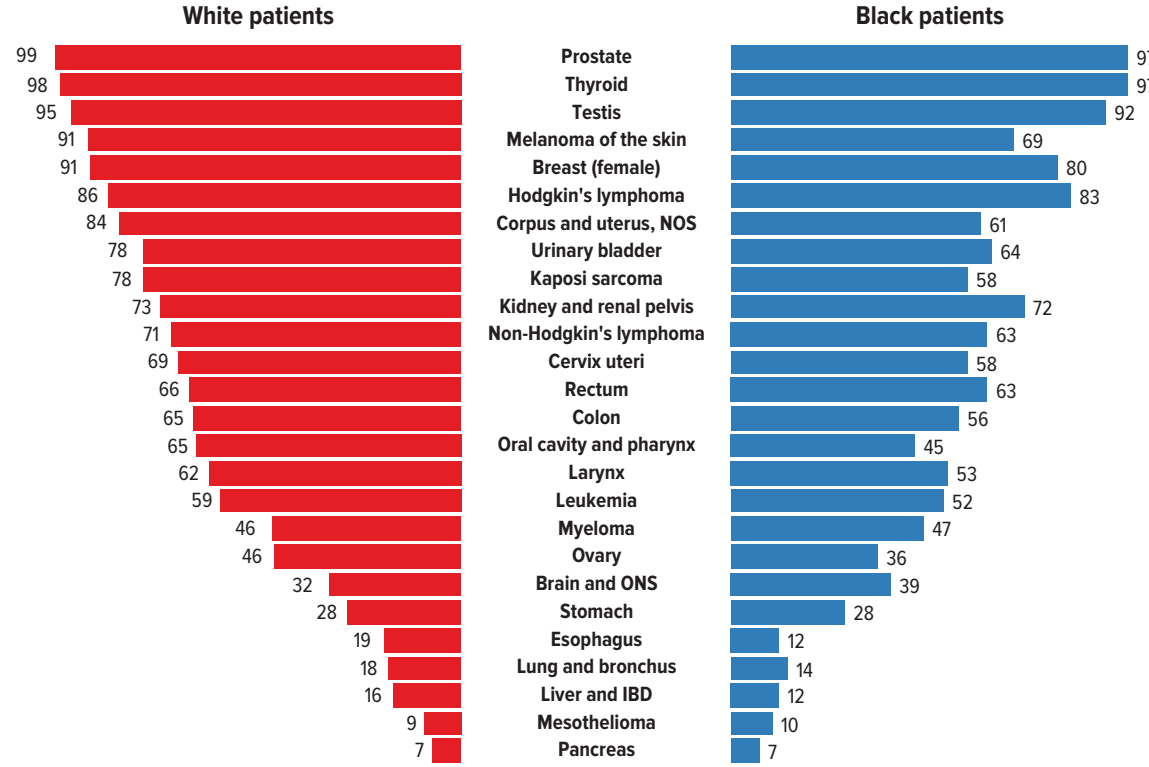
That spending and the focus on immunotherapies, for example, have led to considerable progress in the fight against cancer. The numbers, according to the American Cancer Society (ACS), bear that out (Figure 1). The total cancer death rate rose for most of the 20th century because of the tobacco epidemic, peaking in 1991 at 215 cancer deaths per 100,000 persons. However, from 1991 to 2012, the rate dropped 23% because of reductions in smoking, as well as improvements in early detection and treatment. Death rates are declining for all four of the most common cancer types—lung, colorectal, breast, and prostate.[4]

But the number of annual cancer deaths continues to increase. According to the ACS, about 1,685,210 new cancer cases are expected to be diagnosed in 2016. This estimate does not include carcinoma *in situ* (noninvasive cancer) of any site except urinary bladder, nor does it include basal cell or squamous cell skin cancers because these do not have to be reported to cancer registries. About 595,690 Americans are expected to die of cancer in 2016, which translates to about 1,630 people per day. Cancer is the second most common cause of death in the U.S., exceeded only by heart disease, and accounts for nearly one in four deaths.[4] In 2030, the number of new cancer cases will rise to nearly 2.3 million.

What's more, some types of cancer remain particularly difficult to treat. The five-year relative survival rate for pancreatic cancer, for instance, is just 7%. Not all patients appear to benefit equally from the progress, either: Five-year relative survival for a woman with breast cancer is about 91% if the woman is white, but 80% if the woman is black (Figure 2).[5]

Figure 2 Five-Year Relative Survival (%), National Cancer Institute SEER Program, 2005–2011[5]

Both sexes, by race and cancer site



IBD = intrahepatic bile duct; ONS = other nervous system; NOS = not otherwise specified; SEER = Surveillance, Epidemiology, and End Results.

Source: National Cancer Institute SEER Program. Based on SEER 18 areas (San Francisco [SF], Connecticut, Detroit, Hawaii, Iowa, New Mexico, Seattle, Utah, Atlanta [ATL], San Jose–Monterey [SJM], Los Angeles [LA], Alaska Native Registry, Rural Georgia [RG], California excluding SF/SJM/LA, Kentucky, Louisiana, New Jersey, and Georgia excluding ATL/RG).

Treatment Advances Unquestionably Impressive

Immunotherapies started to have a positive impact on cancer mortality a decade ago with the introduction of interleukin-2. In November 2015, Richard Pazdur, MD, Director of the Office of Hematology and Oncology Products at the Food and Drug Administration (FDA), told an audience at the annual meeting of the Friends of Cancer Research that the agency was on pace to approve 15 new oncology molecular entities in 2015 (it did). That is more than in any year in the past decade (Figure 3).[6] Over the past few years, the all-stars of those new approvals have been antibody immunotherapies, first in advanced melanoma and later in a range of other cancers, including the most common type of lung cancer. These new therapies have significantly extended survival for patients who previously had no effective treatment options. Recent long-term studies indicate that antibody immunotherapies can continue keeping tumor growth in check for years after completion of the treatment. Another kind of immunotherapy, which reprograms the body's own immune cells to attack cancer, is also showing promise in certain blood cancers, as well as in a range of solid tumors.

Recent approval of immune checkpoint inhibitors for the treatment of melanoma and lung cancer has generated a new excitement in the field of cancer therapeutics. The programmed death-1 and programmed death ligand-1 (PD-1/PD-L1) pathway is an important regulator of immune tolerance in the tumor microenvironment. Pembrolizumab is a highly selective, humanized monoclonal IgG4-kappa antibody against the PD-1 receptor that promotes an antitumor immune response by preventing interaction of PD-1 with its ligands PD-L1 and PD-L2. The FDA granted accelerated approval for pembrolizumab in October 2015 to treat patients with advanced non–small-cell lung cancer (NSCLC). Pembrolizumab was already marketed for melanoma, having received an accelerated approval from the FDA in September 2014 for use in patients with metastatic melanoma who were no longer responding to ipilimumab (Yervoy, Merck), the first of the immunotherapies to be approved for melanoma and until recently the standard of care for first-line treatment. Then in October 2015, the FDA approved a new type of immunotherapy for the treatment of advanced melanoma. Talimogene laherparepvec (Imlygic, Amgen) is an oncolytic virus therapy. This is a genetically engineered virus that has been tweaked to preferentially kill cancer cells. In the case of Imlygic, the virus is a modified version of the herpes simplex virus 1, the virus that causes cold sores.

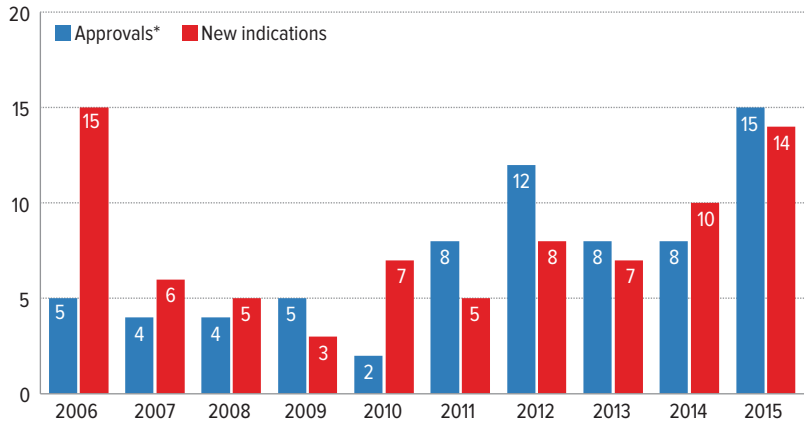
Next-Generation Promise for Immunotherapy

A leading candidate for kicking off the next generation of immunotherapy is called chimeric antigen receptor T-cell therapy, CAR-T for short. After blood is collected from a patient, the patient's T cells are genetically engineered to produce special receptors on their surface called CARs. CARs are proteins that allow the T cells to recognize a specific protein (antigen) on tumor cells. These engineered CAR T cells are grown in the laboratory until they number in the billions. The blood is then given back to the patient. According to the NCI, in several early-stage trials testing CAR-T in patients with advanced acute lymphoblastic leukemia (ALL) who had few if any remaining treatment options, many patients' cancers disappeared entirely. Several of these patients have remained cancer free for extended periods. Equally promising results have been reported in several small trials involving patients with lymphoma.

One CAR-T therapy called CTL019 is apparently furthest along, and has received breakthrough therapy status from the FDA for pediatric and adult patients with relapsed/refractory ALL. Novartis and the University of Pennsylvania Medical School are conducting a phase 2 clinical trial. "With each child we treat as part of this trial, we learn more about the potential of CTL019 to help patients whose cancers cannot be controlled with conventional therapies," says Stephan Grupp, MD, PhD, the Yetta Deitch Novotny Professor of Pediatrics in Penn's Perelman School of Medicine and Director of the Cancer Immunotherapy Frontier Program at The Children's Hospital of Philadelphia. "The response rate and durability we are seeing are unprecedented, and give us hope that personalized cellular therapies will be a powerful key to long-term control of this difficult cancer."

Figure 3 A Decade of FDA Oncology Approvals[6]

The agency's new drug approvals for cancer hit a high in 2015



* Includes new approvals and accelerated approvals of cancer medications and vaccines (e.g., Gardasil), but not medications meant to treat adverse effects of other oncology therapies or help detect cancer.

Source: Food and Drug Administration, hematology/oncology (cancer) approvals and safety notifications

Improvements to the FDA Approval Process

The decisions pharmaceutical companies make about the depth and expense of their research efforts are to some extent tied to what the FDA requires from the company before the agency will approve a new drug. Sundeep Khosla, MD, Dean for Clinical and Translational Science at the Mayo Clinic, says clinical trials are subject to the "Valley of Death." He explains, "This refers to the fact that the average length of time from target discovery to approval of a new drug currently averages approximately

14 years, the failure rate exceeds 95%, and the cost per successful drug exceeds $2 billion, after adjusting for all of the failures." Congress has recognized that equation and has passed new FDA drug-approval methodologies in recent decades. The FDA has also at times acted administratively, on its own authority, to establish new approval programs.

The "fast-track" designation was created in 1997 and is bestowed on drugs that meet two criteria: 1) the drug must show promise in treating a serious, life-threatening condition; and 2) the drug must have the potential to address an unmet medical need, meaning that no other drug or remedy either exists or works as well. 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. The FDA receives approximately 100 to 130 applications a year, and close to 80% will be approved.

The FDA has granted breakthrough therapy status since 2012. Approximately 110 requests have been granted: 50 were for cancer, and 24 of those were immunotherapies (48%) for 15 cancer types—ALL, bladder cancer, brain cancer, triple-negative breast cancer, colorectal cancer, kidney cancer, chronic lymphocytic leukemia, Hodgkin's and non-Hodgkin's lymphoma, NSCLC, melanoma, multiple myeloma, Merkel cell cancer, pancreatic cancer, and sarcoma.

"Breakthrough status allows the FDA to prioritize internal resources and take an 'all hands on deck' approach," notes ASCO's Dr. Schilsky. "FDA is the fastest agency on the planet; no other country is doing it faster." But he adds that the FDA could use more federal funding.

Is More Federal Funding Needed?

The FDA's oncologic drugs section has received escalating funding over the past decade. The division now employs about 70 medical oncologists overseeing the product approval process. In 1999, there were 12 medical oncologists. The moonshot would add $75 million to the FDA's oncology program in fiscal 2017. The new FDA funds, which still need approval from Congress, would help create a virtual Oncology Center of Excellence and new data-sharing initiatives. The virtual center would leverage the skills of regulatory scientists and reviewers with expertise in drugs, biologics, and devices.

Many also argue that the NCI needs more funding after about a decade of flat congressional appropriations that was only partly remedied by a 6% increase for fiscal 2016 to $5.21 billion. The Obama request for fiscal 2017 is $5.45 billion, an increase of $241 million. It is not clear whether that $241 million is part of the $775 million moonshot request for 2017 or is in addition to it.

There is agreement within the cancer research community and in Congress that, besides additional funds, the FDA also needs continuing regulatory reforms such as the earlier ones that allowed for breakthrough therapy status. The 21st Century Cures bill would authorize changes in the FDA and NCI approval and research processes and passed the House in July 2015 with a strong bipartisan vote. However, the Senate Health, Education, Labor, and Pensions Committee has decided to take a different route by approving many separate bills, some of them echoing provisions in H.R. 6, some of them not.

H.R. 6 would provide an additional $9.3 billion in mandatory funding over the next five years to fund the NIH and establish a Cures Innovation Fund to support work toward breakthroughs in biomedical research. It also provides $550 million in added FDA funding over the same period. Those sums would be over and above normal annual appropriations, which is to say major increases in both budgets. But again, these would be increases in the mandatory authorization, not the annual appropriation. The bill is stocked with tens of different provisions, including one to give the FDA even more leeway to approve breakthrough therapies, for example. There are numerous changes to the FDA approval process and the structure of clinical trials, as well as advancement of "precision medicine," which depends on development of a new patient-data network.

Critics of the bill argue the FDA is already the fastest drug-approval agency in the world, and that additional steps to speed new drug approval run the risk of compromising patient safety. Provisions allowing simplification and cost reduction in clinical trials under the NCI's auspices are more universally supported, particularly if they lead to innovative cancer trial structures such as the Lung-MAP clinical trial for patients with advanced squamous cell lung cancer. The trial adapts some of the "precision medicine" techniques endorsed in the 21st Century Cures bill, such as DNA tumor tissue testing leading to biomarker-driven substudies.

Clearly, though, the big issue for the cancer community in 2016 is not the provisions in the House and Senate bill, whenever the latter's form becomes evident, but rather the appropriation of additional funding for the NIH and dedication of a moonshot portion for the NCI.

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