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REPORT



PRECISION ONCOLOGY IN THE ERA OF HEALTH CARE REFORM

IMPROVING OUTCOMES, SUSTAINING
INNOVATION, INCREASING EFFICIENCY

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Foreword

The past decade has seen unprecedented advances in how we diagnose and treat cancer. Cancer is not a single disease: it consists of dozens—if not hundreds—of diseases, defined by genetic mutations driving particular tumor types. When treating a patient, it is now much more routine for oncologists to sequence tumors to identify the best combination of therapies for targeting particular mutations.

As a three-time cancer survivor, I have seen how innovation is affecting the lives of patients and their families: not only do we have more treatment options; the side effects of those treatments are more manageable than ever, and more patients live longer with a cancer diagnosis. As the pace of innovation quickens, we are being flooded with data, in near real time, about the evolution of cancer—even to the individual-patient level. Yet, as Paul Howard observes, data does not automatically translate into knowledge: there is still tremendous variation in patient responses that we don't fully understand; there is a lack of standardization across providers and treatment settings, even when we do have good evidence of “what works”; and there are costs that do not seem proportional to the outcomes that we are able to achieve.

These problems are far from unique to cancer. In fact, they plague America's entire health care system. But cancer is the farthest along in creating a paradigm that we now call “precision medicine”—delivering the right treatment, to the right patient, at the right time. This should be our definition of value. It should also be a basis for rewarding manufacturers, providers, and insurers in a system dedicated to providing the best outcome for each cancer patient, while taking into account his needs, preferences, and goals throughout his treatment journey.

We cannot address rising cancer costs, including drug costs, in a vacuum. We must examine how insurance designs focus attention on short-term costs, not long-term gains for patients and society; we must break down hospital and provider-data silos that keep us from learning as quickly as we can from every patient experience; and we must update outdated federal regulations and, instead, allow expert payers, providers, and innovators to share information and develop new payment contracts, based on real-world data.

We must also not take decades of hard-won progress for granted. All health care stakeholders—insurers, drug companies, regulators, and physicians—have a critical role to play in the adoption of precision medicine. Only by demanding that stakeholders step out of their comfort zone will we be able to agree on a common framework for identifying, measuring, and delivering better value for patients, thereby building on recent progress and accelerating the pace of innovation.

As Howard explains, the heart of this effort will involve turning data into knowledge, enabling patients and physicians to make choices with far greater certainty—after all, we now know that the average patient is not the individual patient. Turning data into knowledge is the greatest step that we can take to determine true value, especially as rising health care spending weighs on the budgets of employers, states, and the federal government. Improving how we research, regulate, develop, deliver, and pay for lifesaving and life-improving cancer treatments will yield enormous dividends—for current and future generations.



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Executive Summary

America is winning the war on cancer, thanks to better prevention strategies, the expanded use of effective diagnostics for detecting cancer at its most treatable stages, and a widening array of powerful new treatments.¹ Most remarkable of all: although age is one of the most significant risk factors for a cancer diagnosis, overall cancer mortality is declining even as we get better at identifying cancers early on.² Researchers are increasingly optimistic that more cancers can be managed as serious, but not necessarily life-threatening, diseases, much as we do for diabetes or HIV.

But the news isn't all good, at least when it comes to health care financing. The list price of newly approved cancer treatments has doubled over the last decade, from \$5,000 to \$10,000 per month.³ While these treatments can be highly effective, overall response rates are still relatively low: only about 20 percent–30 percent of patients treated with new immunotherapies respond to treatment.⁴ Researchers also expect that new drugs will have to be used in combination with other therapies to produce even better outcomes, entailing dramatically increased drug treatment costs. As more patients qualify for treatment with new medicines, U.S. spending on cancer is expected to increase, from \$124 billion in 2010 to at least \$158 billion (2010 dollars) by 2020—a 27 percent increase.⁵ The fastest-growing component of cancer treatment is the soaring cost of new cancer medicines.⁶

As a result, payers are increasingly questioning the pricing of new cancer medicines and are restricting their utilization—especially for non-FDA-approved (“off-label”) indications—often by requiring hefty coinsurance for cancer medicines, sometimes exceeding 30 percent.⁷ In short, patients are being caught between the hammer of rapidly rising drug costs and the anvil of growing cost-control efforts.

Cancer Care in the Era of Health Care Reform

Oncology care isn't the only health care sector where payers are demanding more efficiency, transparency, and accountability for outcomes. America is in the midst of a paradigm shift in how we pay for health care goods and services. The Affordable Care Act (ACA) has committed public and private payers—through a mix of reimbursement changes, regulatory mandates, and taxes—to shifting the U.S. health care system from volume-based reimbursement to a payment system based on value.

Payments to manufacturers of new medicines and medical devices are increasingly bundled with other health care services, putting more pressure on providers to choose the most cost-effective options. Capitated payments to providers on a per-enrollee basis in managed-care organizations also put providers at financial risk for managing patients with high-cost conditions, such as cancer, centralizing purchasing decisions, and highlighting the importance of comparative effectiveness data. Bonuses are also paid to providers who adhere to certain process metrics, or achieve certain outcomes (say, controlling a diabetic's blood sugar, reducing hospital readmissions, or reducing avoidable hospital or emergency-room use). And Medicare wants 85 percent of fee-for-service care under value- or outcomes-based contracts by 2018.

The hope is that new payment models will encourage providers to focus on care coordination, standardize the use of evidence-based treatments, and, along with targeted patient cost-sharing, encourage patients to seek treatments that are more cost-effective.⁸ While direct oncology care accounts for only about 5 percent of total U.S. health care expenditures,⁹ it is one of the fastest-growing components and is an area where the cost of care doesn't always seem to be associated with better health outcomes. As researchers in a *Health Affairs* blog wrote in 2015:

Adherence to treatment guidelines and quality remain highly variable across providers in a wide variety of oncology domains, including end-of-life care,¹⁰ prostate cancer,¹¹ ovarian cancer,¹² and colorectal cancer screening.¹³ Problems range from underuse of highly effective therapies and procedures to overuse of ineffective ones. Thus, while today's typical cancer patient is likely better off than her counterpart from earlier years, not all patients are receiving the most effective care.... Rewarding physicians for patient health improvement moves physician incentives closer to the values and needs of patients.¹⁴

While the desire to shift payment from volume to value is laudable, it will have to be carefully considered in light of the fact that there is wide variation in how patients with the same nominal cancer diagnosis (say, lung cancer) respond to treatment: cancer, we now know, isn't one disease but dozens, if not hundreds, of different diseases. Cancer is a disease defined by aberrations

in the genetic mechanisms controlling cell proliferation and growth; as a result, no two tumors in the same patient may be alike, let alone across hundreds or thousands of patients.

For instance, breast cancer is at least ten different diseases;¹⁵ prostate cancer, five diseases. Lung cancer may be dozens of different diseases.¹⁶ Rare genetic mutations have been found to be present in small percentages of cancer patients across many different tumor types; ultimately, cancer may turn out to be a large constellation of what are, in fact, small clusters of patients with similar molecular profiles.¹⁷

Cancer is also notoriously adaptive, often evolving to evade the drugs and radiation treatments designed to eradicate it. Most cancers are curable—largely through surgery or radiation treatment—if caught early enough; but once they have metastasized, they can be exponentially more difficult to treat. Even when cancers respond to initial treatment, shrinking or disappearing dramatically, they can surge back from a few surviving tumor cells months or even years later with great lethality.¹⁸ While treatments for some cancers, especially some blood cancers and testicular cancer, have been successfully standardized with very high cure rates (imatinib is effectively a functional cure for many patients with chronic myelogenous leukemia; non-Hodgkin's lymphoma and the most common childhood leukemias are eminently curable, too), these cases are the exceptions.

In short, we are likely to have much greater success standardizing care for cardiovascular disease or diabetes over larger populations, at least compared with cancer. The risk factors for the former are well known and easily tracked in real time through low-cost diagnostics (measuring hemoglobin A1c or high cholesterol through small blood draws), and mortality for these diseases accrues over years and decades, not months. In terms of its complexity and fearsomeness, cancer is, indeed, the emperor of all maladies.

As a result, when it comes to cancer, we must be cognizant of the fact that one size rarely fits all, or even most.¹⁹ The danger: even as researchers and companies develop treatments for cancer patients that are more personalized and target tumor cells' unique characteristics, additional progress might be delayed or derailed by new payment models that focus on drug prices in isolation or that lock in bundled-payment rates based on existing technologies, without considering: the reduced costs that might occur downstream (such as fewer hospitalizations or ER visits); the increased productivity as cancer patients return to work; the reduced burdens on caregivers; or the possibility of one-shot cures, like chimeric antigen-receptor T-cell therapies, whose benefits may last for decades.

Of course, we should not expect every medicine to save the health care system money. Ironically, allowing cancer patients to live longer—or even curing them—is apt to cost us more money simply because more patients will become treatable and will remain responsive to treatment for longer periods.

A value-based health care system for oncology should instead focus on the holistic impact that medicines can have over their effective life cycle (i.e., as long as they remain therapeutically relevant) within an efficient, evidence-based oncology care ecosystem. Pricing can, and should, evolve to reflect knowledge of other therapeutic options, patient preferences, and the value delivered to patients with a given disease state.

What we want is a learning health care system that captures evidence on the full impact of incremental and breakthrough innovations across the continuum of oncology care throughout the patient's cancer journey. This approach, if done transparently and with full patient engagement, will better align product prices with value, especially through market competition; will encourage delivery-system reform to improve the standard of care delivered to each patient; and will reassure payers that they are achieving better outcomes for every dollar spent on cancer care.

Can We Deliver High-Value, Highly Customizable Cancer Care at Scale?

The real challenge with cancer care is delivering personalized care at scale—"precision oncology." From Amazon to Wal-Mart, American companies have learned to utilize real-time data to enable just-in-time manufacturing, to tailor product development and marketing, and to empower constant quality-improvement efforts. Along the way, American companies have dominated the commanding heights of the global information economy and transformed entire industries, from finance to retail sales.

Critically, the Amazons and the Googles of the world have helped pioneer the field of Big Data analytics and are looking to extend their expertise in data aggregation and analytics to health care, especially cancer genomics.²⁰ Nimble start-ups focused on cancer informatics are also making their mark. Flatiron Health is developing an electronic health-record system that can link cancer centers and community oncologists across the U.S., allowing deeper analysis of patient outcomes (including side effects) and total cost of care, as well as the ability to automatically flag patients for inclusion in clinical trials. Flatiron can also help manufacturers identify potential new targets for drug development by linking genomic data with clinical outcomes. Similarly, Sage Bionetworks is using its informatics platform, Synapse, to

create a collaborative hub for analysts/programmers and clinicians, helping to share data-research assets.²¹

As access to high-quality oncology data and analytics improves, in real time and at the point of care, we have an opportunity to learn from every treatment decision and patient interaction so that we can improve outcomes and deliver better value across the entire cancer care ecosystem. As Amy Abernethy, chief medical officer and senior vice president for oncology at Flatiron Health, states:

With personalized oncology ... doctors would tailor treatments to individual patients and their diseases based on real data on what works and what doesn't in specific circumstances. Personalized medicine means putting the person back at the center—and moving beyond hunches to incorporate all types of data to make better clinical choices in a true evidence-based practice.²²

This is a bold, achievable vision that will require greater cancer data-sharing than we currently have. Unfortunately, much of that information is trapped in electronic health records that don't talk to one another or are unavailable in a standardized form that could be plugged in to a database.

Robust data-sharing of patient outcomes, combined with genomic and phenotypic data, can accelerate the advent of precision oncology—delivering the right treatment, at the right time, to the right patient; it can also serve as a platform for value-based reimbursement contracts that better align price with value by collecting data on critical metrics (survival, quality of life, major side effects) with much greater granularity. As a result, we can make technology and delivery-system assessment much more routine, not only for medicines but for every component of oncology care, including hospitalization/ER use, radiology, surgery, and palliative care.²³ This can give all stakeholders—insurers, innovators, regulators, patients, and policymakers—a common foundation on which to build a continuously improving oncology care system that better aligns spending with value.

Toward Real-World Data

Insurance coverage has typically followed FDA approval after a sponsor demonstrates safety and efficacy in “adequate and well-controlled” clinical trials. However, only a small fraction of cancer patients (typically, 3 percent–5 percent) participate in clinical trials, limiting insurers' ability to generalize these results to patients who may be significantly sicker or older than those who enroll in trials.

The FDA's increasing use of molecular biomarkers (such as Her2Neu for breast cancer) and surrogate endpoints (such as time to tumor progression) in expedited-approval programs has made it more challenging for insurers to assess the value of treatments approved after early-stage trials in small numbers of patients. More of the onus for evidence supporting safety and efficacy in broader cohorts of patients for newly approved cancer medicines, especially for “off-label” uses, is being shifted to the real-world environment: the value of new treatments will be an evolving equation, rather than one simply set in stone at the time of launch.²⁴

Technology assessment in a complex, rapidly changing technological environment requires a comprehensive analysis of all the benefits, risks, and costs that adhere to a given treatment choice, to a given set of patient preferences (which may vary with age, stage of disease, and risk tolerance), and to a given treatment setting (freestanding oncology clinic versus hospital outpatient). Most important, it requires a trusted “data commons” that allows stakeholders to reach agreement on metrics for assessing—and then rewarding—value that reflects real-world patient outcomes.

Informatics and postmarket surveillance, however, can help stakeholders transition away from traditional, premarket trials for demonstrating safety and efficacy, and toward well-designed observational studies that evaluate product performance in the real world.²⁵ This should make results more generalizable and should support outcomes-based contract designs that reflect the value delivered to patients.

Robust informatics systems for oncology-technology assessment can allow us to move from population-level averages to better assessment at the individual level, allowing physicians and patients to make more informed, granular decisions that increase the value delivered by health insurance and overall health care. The resulting standard of care will become increasingly nuanced, especially if payment systems reward outcomes and shared decision making with patients.

Outcomes-based payments can also help create a much needed business case for providers and innovators to focus on the nuts and bolts of precision oncology, including assay standardization, creating high-quality tumor and biospecimen repositories, and validating new oncology biomarkers and surrogate endpoints. Understanding who will respond—and why—will be key to securing timely payment, as well as premium payments for breakthrough cancer innovations.

Without a robust, democratized informatics environment for oncology, patient cost-sharing or prior-authorization requirements will continue to be used as one-size-fits-all utilization-management tools. Real-time technology assessment and outcomes-based reimbursements can lower barriers to the appropriate use of medicines by sharing financial risk with innovators and providers. All oncology stakeholders will have to reset their expectations for rewarding value and adapt to a more intensive role for utilizing real-world data throughout premarket drug development and post-launch.

The key challenge will be to ensure that the aggregation, collection, and curation of oncology data don't add to already onerous administrative burdens on oncologists. However, given the many constraints already facing oncologists, informatics might reduce those burdens by helping insurers and innovators converge on clear, outcomes-based payment systems.

Cutting the Gordian Knot Between Innovation and Technology Assessment

Medical progress and technology assessment need not be pitted against each other. This paper makes the case for a new social contract for oncology drug development and reimbursement that can ensure that we accelerate the adoption of the right treatments (whether branded drugs, generics/biosimilars, or repurposed medicines) to the right patients, while also experimenting with delivery-system reforms (including episode bundles and oncology centers of excellence) that may offer greater value to patients for every dollar spent on care.

Central to this effort will be regulatory reforms needed to accelerate outcomes-based contracting, especially the creation of safe harbors from federal regulations governing "best price," anti-kickback, and off-label prescribing. As technology advances, we will also have to consider new financial strategies for rewarding innovators who develop truly disruptive innovations, such as chimeric antigen-receptor therapies and gene therapies that may represent cancer cures. Doing so may include amortization of drug costs (medical mortgages for patient cost-sharing) or other approaches to risk adjustment that allow the costs of breakthrough innovations to be shared over more lives and for longer periods.

We should not underestimate the challenges in moving from a reimbursement system based on volume to one based on real-world outcomes. But these challenges can be overcome if stakeholders and policymakers are serious about putting

patients first and embracing the full potential of precision oncology to revolutionize cancer treatment. **This paper concludes with the following recommendations:**

1. Develop the IT systems, including data enclaves and patient registries, to better capture the full costs and benefits of different treatment and delivery approaches across a given disease state.
2. Accelerate regulatory reforms that lower the costs and risks associated with oncology drug development and encourage drug repurposing.
3. Make a greater commitment to survey and incorporate patient preferences throughout the oncology care continuum.
4. Embrace novel reimbursement strategies, but don't expect one size to fit all.
5. Create an FDA safe harbor for off-label prescribing.
6. Allow novel value-based contract designs to operate outside the Medicaid best-price construct.
7. Create a safe harbor from federal and state anti-kickback statutes.

PRECISION ONCOLOGY IN THE ERA OF HEALTH CARE REFORM

IMPROVING OUTCOMES, SUSTAINING INNOVATION, INCREASING EFFICIENCY

I. Introduction

The U.S. is the global leader in cancer research and drug development. The federal government devotes over \$5 billion²⁶ annually to researching the basic biology of cancer. A survey published in 2005 found that the U.S. spends about five times more than the E.U.²⁷ on noncommercial cancer research; venture-capital investors and drug companies—including many biotech start-ups spun out of university research labs—invest in testing and developing hundreds of potential anticancer treatments; the National Cancer Institute maintains a network of cancer centers that enroll tens of thousands of patients into trials each year.

America's commitment to the war on cancer reflects the burden of the disease. It is the second leading cause of death: in 2016, 1.7 million Americans will be newly diagnosed with cancer, with nearly 600,000 succumbing to it.²⁸ By 2030, cancer will likely become the leading cause of death, largely due to the aging of the U.S. population. Yet better detection and treatments mean that more Americans are surviving a cancer diagnosis, with cancer survivorship exceeding 14 million people in 2015.²⁹ More than two-thirds (68 percent) of Americans diagnosed with cancer can expect to live at least five years, up from just 50 percent in the 1970s.³⁰ Progress against the disease has been broad and is accelerating (**Figures 1–3**).

FIGURE 1. Source: American Cancer Society

U.S. Cancer Incidence and Mortality, 1975–2012

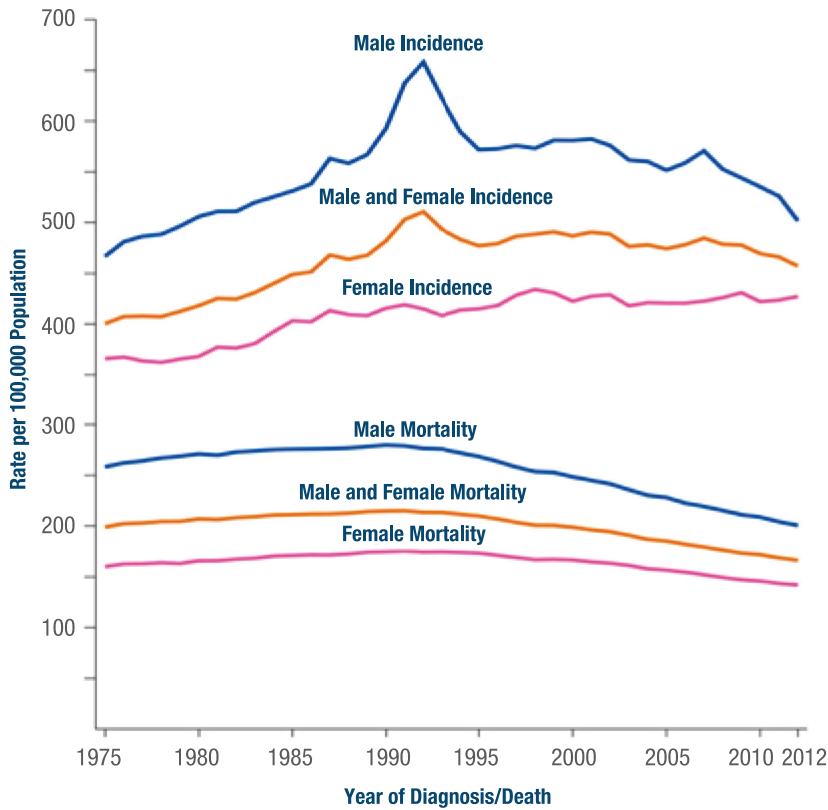


FIGURE 2. Source: Health Affairs³¹

Life Expectancy After Cancer Diagnosis, U.S. v. Europe, 1983–99

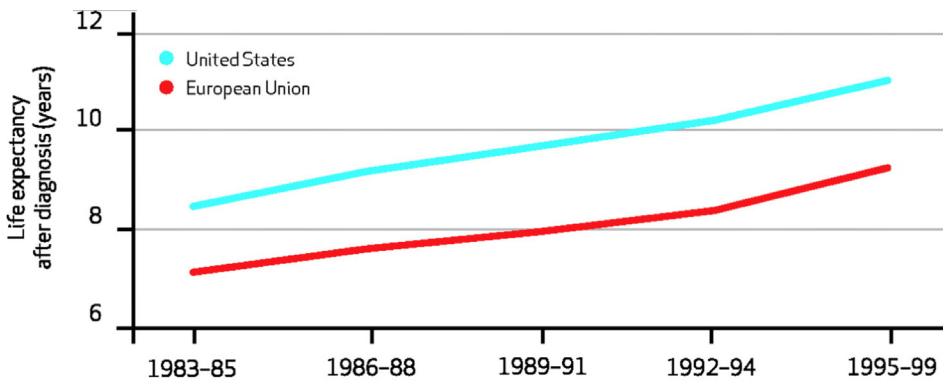


Figure 3. Progress in the War on Cancer

- ◆ Since 1991, cancer mortality has fallen by 23 percent; since 1995, cancer mortality has dropped by 1.8 percent per year for men and 1.4 percent for women.³²
- ◆ During 1990–99, cancer mortality rates fell by 7.5 percent; during 2000–11, they fell by 15 percent.³³⁻³⁴
- ◆ Female breast cancer mortality has declined by 36 percent from its 1989 peak; prostate and colorectal cancer mortality rates have fallen by about 50 percent from their previous highs.

Source: American Cancer Society's Cancer Facts & Figures 2016

Prevention efforts deserve much credit for the improving outlook for American cancer patients. Antismoking campaigns have gradually reduced U.S. smoking rates to among the lowest in the developed world, sharply reducing the incidence of lung cancer. But the benefits of improved detection and treatment cannot be overemphasized. Oncologists have learned how to combine incremental and breakthrough innovations in cancer treatment to gradually produce significantly better outcomes for many common cancers and to reduce the harsh side effects associated with cancer treatment. True cures have also emerged: testicular cancer is almost completely curable,³⁵ as are the most common types of childhood leukemia³⁶ and many adult lymphomas.³⁷

These advances have delivered enormous economic value to society. Kevin Murphy and Robert Topel of the Uni-

versity of Chicago have estimated that every 1 percent reduction in cancer mortality is worth about \$500 billion.³⁸ Cancer mortality has fallen by 23 percent over the last two decades,³⁹ creating more than \$10 trillion in economic value for society.

The Dawn of Precision Oncology

Cancer is a genomic disease, defined by aberrations in the genetic and molecular mechanisms that control cell growth and proliferation. But when the war on cancer started in 1971, cancer genetics was basically terra incognita. Today, new tools, such as genomic and proteomic screening, structure-based drug design, and gene-editing techniques provide a vastly improved understanding of the genomics of cancer.

Clinicians can now build something akin to a Google Maps for tumor growth, enabling more personalized and less toxic approaches to treating the disease. As Vincent DeVita—a leading oncologist who pioneered the development of several successful multidrug cancer therapies, including treatments for leukemia and Hodgkin’s lymphoma, and who served as director of the Nixon-era National Cancer Program and, more recently, of the National Cancer Institute—notes in *The Death of Cancer*:

The hallmarks of cancer ... are acquired characteristics that cancer cells need to survive and grow. Without them, cancer cells are not a threat to life. Prevent them from developing, and a normal cell will not become a cancer cell. Get to a growing tumor mass before it fully develops all the hallmarks, and it can be cured by local means like surgery or radiotherapy. Shut these hallmarks down in a metastatic cancer, and a growing cancer is stopped in its tracks. We are now able to do all of the above.⁴⁰

Some of these advances would have been considered science fiction only a decade ago. Advances in molecularly targeted therapies now allow us to fine-tune treatments to attack cancer-promoting pathways while largely sparing healthy tissue. New immuno-oncology therapies are harnessing patients’ own immune systems to recognize and destroy cancerous cells. Several companies have demonstrated that genetically reengineered human T-cells can recognize cell-surface antigens on cancer cells, producing prolonged remissions in patients with drug-resistant blood cancers. In 2015, the FDA approved the first virus designed to attack cancer (glioblastoma); numerous cancer vaccines are in development, too.

Since 2011, the advent of new immunotherapies, “checkpoint inhibitors,” has delivered extraordinary outcomes for some hard-to-treat solid tumors, including lung cancer and metastatic melanoma. Former president Jimmy Carter, diagnosed

with melanoma that had metastasized to his brain, recently declared that his disease was undetectable after being treated with radiation, surgery, and pembrolizumab, one of the most recently approved checkpoint inhibitors.⁴¹

Though not every patient will respond to immunotherapies, those who do respond have seen durable responses—and even remissions that last for months or years, not weeks. For instance, until recently, there were few effective treatments for advanced non-small-cell lung cancer (NSCLC). The few chemotherapy drugs that are effective, such as docetaxel, produced negligible gains in survival. The 2015 approval of nivolumab, a checkpoint inhibitor in a new class of drugs (PD-1/PD-L1 inhibitors), has changed this dramatically. In a follow up to two pivotal trials leading to its approval, close to 30 percent of NSCLC patients were still alive 18 months after treatment with nivolumab, compared with just 13 percent of patients on chemotherapy.⁴²

Another study showed the potential of genomic screening to help match new therapies with patients who are most likely to respond: 20 percent of colon cancer patients with “mismatch-repair deficiency,” a breakdown in the genes that prevent genetic mutations, had a much greater response rate (40 percent) to pembrolizumab; patients whose tumors did not have the deficiency saw no benefit. Further, disease-control rates were 92 percent for those with mismatch-repair deficiency and only 16 percent for those without it.⁴³

Chimeric antigen-receptor therapies (CAR-T) have also demonstrated remarkable efficacy in some blood cancers. Juno Therapeutics recently released data on two CAR-T products in development. One product produced complete responses in 57 percent of leukemia patients and 64 percent of lymphoma patients.⁴⁴ Another product achieved an 82 percent complete-response rate in patients with acute lymphoblastic leukemia.⁴⁵ (A “complete response” means that the cancer has disappeared, though it does not mean that the patient is necessarily cured.) But the potential for producing durable remissions, or even cures, in a subset of heavily pretreated patients from a single treatment is a remarkable innovation and may augur a time when such treatments are first-line therapies.

Treatment is not the only place where the pace of progress is accelerating. Illumina, one of the world’s largest makers of gene-sequencing technology, recently spun off a company, Grail, focused on developing a test to detect tumor DNA in a patient’s bloodstream before tumors are detectable using conventional imaging tests. Because cancers are most curable—typically, through surgery or radiation treatment—when they

are caught early, companies such as Grail represent an enormous opportunity to spare millions of patients the serious side effects and financial burdens associated with cancers that are diagnosed only after they become life-threatening.

With a growing armamentarium of effective treatment approaches, researchers believe that it may be possible to manage cancer as a serious chronic disease, similar to how HIV/AIDS and diabetes are treated today. Combination therapies can help hold the disease in check for years, perhaps decades, without necessarily being able to eliminate it entirely, while also preventing the emergence of drug resistance. Precision oncology—delivering the right treatment, to the right patient, at the right time—will be at the heart of this strategy.

While precision oncology is still in its infancy, it is advancing rapidly. Since the deciphering of the human genome in 2000, the costs and time required to sequence the human genome have fallen by over a million-fold. (Sequencing the first human genome took about \$2 billion and a decade; next-generation sequencing platforms can perform far more reliable sequencing at a cost of \$2,000 in less than a week.) Costs continue to fall even as the speed and reliability of sequencing increase.

As a result, tumor sequencing is becoming an increasingly routine part of clinical cancer care. For example, by sequencing a patient's tumor and comparing it with healthy DNA from the same patient, physicians and researchers can hone in on the driver genes responsible for launching and sustaining malignancy, as well as search for drugs that may inhibit those pathways—whether FDA-approved, available through a clinical trial, or an off-label treatment based on the drug's known mechanism of action.

New Hope but Also New Financial Challenges

From a financial and treatment perspective, the challenge with this approach is that cancer is being fractionalized from one disease into hundreds of smaller orphan diseases, with populations ranging from a few hundred to tens of thousands. Treatment costs are rising as more patients become eligible for new targeted treatments or immunotherapies, and remain on them for longer periods. At the same time, the evidence base for treatment outside the FDA label, or compared with other treatment strategies, may be lacking or uncertain. We should not assume that newer is always better, or that molecularly targeted therapies will automatically be effective across different tumor types.⁴⁶ We still have much to learn about tumor biology and its evolution in response to treatment.

The varying quality of sequencing platforms and tumor biopsies is another serious concern. If the correct gene is not identified, patients might be denied effective therapy because they can't afford to pay for it out of pocket—or, conversely, patients

might receive serious health risks from the therapy without any hope of benefit. Without more high-quality biomarkers to guide treatment, patients and physicians are making high-cost, high-stakes decisions without good guide rails. Even with high-quality sequencing platforms, physicians may not know how to incorporate the results into patient care because they lack confidence in their own ability to correctly interpret genomic data. Indeed, in 2014, the *Journal of Clinical Oncology* reported:

[T]here is little consensus on how physicians plan to use somatic predictive multiplex genetic testing in practice or in their attitudes about test result disclosure. Our data also suggest that genomic confidence may be highly variable among cancer physicians and that genomic confidence might be an important factor in test adoption decisions. *These data suggest the value of evidence-based guidelines to help physicians determine when genomic testing is indicated and renewed efforts in physician genomic education and decision support.*⁴⁷ (emphasis added)

As the stakes and costs associated with cancer treatments keep rising, especially for patients (**Figure 4**), the reality is that no single oncologist can keep up with the state of the art on his own, resulting in a potential gap between the quality of care delivered in the best cancer centers and that received by the majority of patients (especially for hard-to-treat cancers) who are treated by community oncologists. Patients and physicians may also have to navigate complex insurance-coverage policies when drugs are used off-label. In its 2016 report on the state of cancer care in America, the American Society of Clinical Oncology observed:

High unit cost and inconsistent reimbursement policies across payers hinder patients' access to immunotherapies. Emerging data suggest that using drugs in combination and at higher doses increases efficacy, making the prospect of an unsustainable financial burden—for both individual patients and the system—more likely. For example, a combination of nivolumab and ipilimumab was approved for melanoma in October 2015, with an annual cost of more than \$250,000 per patient. Former President Jimmy Carter, who was diagnosed with advanced melanoma in August 2015, announced in December that he is cancer free after immunotherapy with pembrolizumab, which costs \$150,000 per year. It is unclear if patients or payers can afford these treatments or whether the health system is able to offer them and remain financially sound. Efforts to reform payment and identify high-value treatments will be essential to integrating immunotherapies into routine practice in a thoughtful manner.⁴⁸

Figure 4. Securitizing Health Care Loans

Many cancer therapies represent incremental advances over existing standards of care, at least for the average patient; but rapid advances in technology, particularly surrounding immunotherapies, offer the possibility of significant advances or even cures for at least some types of cancer. Chimeric antigen-receptor therapies for blood cancers have shown high rates of complete remissions in early- and mid-stage trials and are apt to be commercialized in the near future. Gene-modulating approaches, such as CRISPR/Cas9, could allow enhanced efficacy of existing treatments or, alternatively, silence multiple tumor-promoting pathways.⁴⁹ However, prospective gene-therapy cures for rare pediatric diseases have been estimated to cost upward of \$1 million.⁵⁰

In a recent perspective in *Science Translational Medicine*,⁵¹ researchers from MIT and Harvard simulate a strategy for securitizing the cost of expensive, curative therapies to offer broader access to all patients who are eligible for treatment. The researchers propose two approaches. In the first, patients' out-of-pocket costs would be covered through a health care loan (HCL) offered through a "special purpose entity" (SPE), much as home mortgages are covered today. The patient would borrow from the SPE, and the loan would be amortized over some repayment period, with interest rates designed to make the SPE attractive for investors. Investments, in the form of equity and debt issuance, would fund the SPE. In support of outcomes-based payment arrangements, payments to the pharmaceutical firm would be discontinued in the event of a consumer default, defined as death, end of effective response to therapy, or bankruptcy. Insurers would continue to cover the remaining cost of the drug (assumed to be roughly 50 percent in the researchers' example).

From the goal of maximizing alignment between innovation, access, and pricing competition, two important advantages may accrue to this model. Larger patient pools of eligible consumers may give more bargaining power to insurers to lower drug prices. Because the full payment would accrue only over the life of the loan, drug companies would have a greater incentive to invest in the development of curative therapies and to ensure that patients remained compliant and healthy over the life of the loan. Access to a variety of different therapeutic approaches, under different loan terms, could help spur further competition based on patient adherence, or ease of administration.

To spur widespread uptake across low-income consumers, third parties—such as philanthropists, patient-advocacy groups, government agencies, insurance companies, and even pharmaceutical companies—could guarantee the loans. (The researchers expect that such guarantees would be a small percentage of the face value of the bonds [about 0.006 percent under a pessimistic scenario].) However, the researchers make clear that securitization is a second-best solution:

Large copays are antithetical to the very purpose of health insurance. Hence, our proposal for patients to cover these costs with [health care loans] is only a short-run bridging solution. A more sustainable and economically more efficient approach to address the high cost of transformative therapies is for insurance companies to cover these costs, spread the amortized costs across their policyholders, finance the upfront payments using securitization, and set premiums at the appropriate levels to cover these costs.⁵²

This second approach would see insurers, not patients, take on health care loans, adjusting premiums as necessary to spread costs among policyholders. For curative treatments that might cost a million dollars or more (Glybera, in the researchers' example), patient-level HCLs would not be feasible, and the second approach would be the only viable one. In the U.S. system, a major barrier to this latter approach is the rapid switching of policyholders across plans, particularly in private-employer and exchange markets. However, regulation could address this uncertainty by requiring the new insurers to "assume the remaining amortized debt obligations of new policyholders who are switching plans.... [I]f a policyholder switches from insurer A to insurer B today, and was the recipient of a transformative therapy 3 years ago that insurer A amortized via a 9-year HCL, insurer B would be required to assume the payments of this HCL over the remaining 6 years for this policyholder as part of the switch."⁵³

The researchers note several potential barriers and uncertainties associated with this approach, not least the ethical implications of denying access to potentially curative therapies based on ability to pay. Yet for patients who now face high co-pays or coinsurance, this concern already exists; even in single-payer systems, denying coverage based on the average cost-effectiveness of the therapy remains a barrier to access, particularly for patients who benefit more than the average.

Pricing Signals Drive Investment and Innovation—and Can Also Drive Competition

Concerns about drug pricing should not be dismissed; but drug prices must be understood in the context of how pricing signals for oncology medicines attract ongoing investment. The cancer-drug pipeline reflects America's attractive pricing and investment environment for oncology. Oncology is the recipient of the largest share of U.S. life-sciences venture-capital funding (\$9 billion), accounting for nearly a quarter (24 percent) of all venture investment in the life sciences. Treatments for neurology (12 percent) and infectious disease (10 percent) claim a distant second and third place, respectively.⁵⁴

Over time, greater investment translates into more treatment options for patients. For instance, in its 2014 oncology drug report, the IMS Institute for Healthcare Informatics reported that cancer treatments account for more than 30 percent of all compounds in early-stage clinical trials.⁵⁵ During 2010–14, the FDA approved 37 cancer drugs, nearly doubling the 19 medicines approved during 2005–09.⁵⁶ In 2015, 14 of the 45 drugs approved by the FDA were for cancer indications. As of late 2015, more than 1,000 medicines were in development for cancer.

The current pipeline may heighten pricing concerns further, with the prospect of a flood of six-figure cancer drugs entering the market over the next decade. However, many of these medicines will be targeting the same indications and even the same molecular targets. According to a 2015 study from researchers at MIT, only 12 of 141 compounds (8.5 percent) in Phase III testing faced no competition from another product: “[Oncology] developers appear likely to face competition not only after they reach the market, but in their quest to be first in class.”⁵⁷

This presents an unprecedented opportunity to drive competition based on value. Advances in electronic medical records—and the potential for large linked databases that contain information on patients' tumors, clinical outcomes, and even claims costs—offer the potential to use the large numbers of medicines in development to accelerate the adoption of precision oncology, as well as to improve competition based on real-world outcomes, including the costs attributable to side effects, hospitalizations, and/or improved adherence and quality of life for patients.

It is also important to note that precision oncology may not require newly approved, or even branded, medicines. Precision oncology should allow us to identify cohorts of patients who can be cured, or do better with, standard approaches (patented or generic); to identify medicines that can be repur-

posed from other indications to treat cancer;⁵⁸ and to develop a robust understanding of the costs and outcomes for select patient cohorts that enable outcomes-based reimbursement contracts and novel payment strategies that share risk among stakeholders based on delivering better outcomes.

Ideally, discussion about outcomes-based contracts between payers, innovators, and providers would begin before a product is approved by the FDA—leading to greater financial predictability for payers and innovators after the product is approved and fewer initial access barriers for patients. This can create a “win-win-win” scenario for payers, innovators who deliver value, and, most important, patients. How we move toward these arrangements is the challenge we will consider next.

II. Building the Infrastructure for Precision Oncology and Outcomes-Based Reimbursement

Shifting from volume to value in oncology through outcomes-based reimbursement requires agreeing on a baseline data infrastructure (key metrics) to help payers, providers, and innovators link the use of a drug with patient outcomes (response to therapy, adverse events or hospitalizations, mortality) and to enable physician access to high-quality analytics. Depending on the outcome and contract terms, the insurer would then pay for the result or incur a rebate from the manufacturer. Drug companies would accept greater financial risk for ineffective treatments.

Oncologists and their patients would begin their treatment dialogue by consulting large databases that included the latest National Comprehensive Cancer Network guidelines, emerging data on real-world outcomes (including benefits and side effects), and patient cost-sharing (if any). Decisions would continue to be guided by patient preferences, which may

change throughout the cancer journey. The final decision of the patient, along with longitudinal outcomes, would then be seamlessly uploaded into the database to improve the evidence base for the entire oncology community.

Rewarding Real-World Learning

To avoid penalizing oncologists who are treating patients with rare or refractory cancers, stakeholders should also be cognizant of structuring pay-for-performance contracts so as not to discourage experimentation—especially when we know that no biomarker test or algorithm will be able to separate potential responders and nonresponders with 100 percent accuracy.

Take pancreatic cancer. With few good options available when the disease is not caught early, we should reject a reimbursement system that views the absence of current evidence supporting a novel treatment approach as a pretext for therapeutic nihilism. If we did, diseases like childhood leukemia, adult lymphomas, and testicular cancer would never have been cured.

However, in these cases, patient inclusion in disease registries and clinical trials (including observational trials) should be considered standard of care. Ideally, electronic medical records should support automatic notification of when patients are eligible for clinical trials, with minimal barriers for inclusion/exclusion criteria. For instance, patients receiving off-label therapies might be enrolled in clinical trials where the cost of an experimental drug is covered, such as the American Society of Clinical Oncology and Syapse’s TAPUR trial.⁵⁹

When clinical trials are not available, physicians could prescribe the drug with the understanding that only a fraction of the drug cost would be reimbursed by the payer. However, in the event that the patient responded—compared with the current standard of care or no treatment—the payer could agree to reimburse more than the average sales price, perhaps at 125 percent. The top-up payment would help compensate oncologists for developing new treatment protocols for hard-to-treat cohorts of patients.

Outcomes-based contracts would also encourage innovators to invest in developing high-quality biomarkers and standardized assays (whether lab-developed tests or companion diagnostics) that could rapidly detect high responders and help expand the drug’s label. Further, outcomes-based contracts would help provide a much needed “business case” for oncology data-sharing, as urged by many in the oncology community: “[A] partnership of government, payers, providers, patients, and health IT developers working together to achieve common goals is possible if there are mutually aligned incentives, such as the ideas embodied in value-based purchasing/MACRA.”⁶⁰

Collaboration on Standards for Data-Sharing, Data Aggregation, and Data Curation

The critical elements of an outcomes-based reimbursement system in oncology are:

1. Stakeholders reaching clearer definitions of what “success” means in a given context.
2. Reliable data- and decision-support tools to help physicians and patients gauge the likelihood of success from a given treatment choice.
3. Real-time data, transparently available, on drug performance in similar cohorts of patients that help to create a positive feedback loop for clinical and preclinical research.

Stakeholders must work together to develop key metrics and data-sharing protocols. Each sector holds critical data that can improve the functioning of the whole. Insurers have access to robust claims and cost data; providers have access to vital clinical and outcomes data, much of it in unstructured formats like radiology scans; and innovators collect voluminous off-label information on the effects and pharmaco-economic performance of their medicines. A greater effort, too, must be made to incorporate patient preferences into drug development and real-world data collection through patient, or caregiver, reported outcomes.

The most important step is a commitment to greater data-sharing and data aggregation across disparate health care systems. No single cancer center or researcher holds the key to curing cancer—but incentives to share data are weak. We must develop the incentives, including carrots and sticks, that strongly encourage researchers and providers to share data in real time.⁶¹ Value-based contracts should encourage providers to share data while competing on outcomes and analytics. A democratized approach to oncology data could be created through a data enclave that would operate as a digital-rights manager for contributors to the enclave. As Newman et al. write in *Health Affairs*:

The resources exist to access and analyze extremely large health datasets in the secure, HIPAA compliant, computing environments of data enclaves. Data enclaves⁶² are a secure computing environment, firewalled from outside intrusion, accessible only by authorized users, that allows for remote access to microdata where the inflow and outflow are controlled and monitored by either experienced confidentiality officers or by algorithms, whereby users have access to analytic tools and only those data they are licensed to use.⁶³

An oncology-data enclave would house structured and unstructured data from contributors, along with analytics platforms that allow the data to be queried based on standardized licensing agreements. Licensing fees could vary based on the size or quality of the data accessed; on one-time fees or annual subscriptions; or on fractional royalties from FDA-approved products developed using accessed data sets. Royalties would flow to the institutions whose data was accessed and used in subsequent regulatory applications, and would support future cancer research efforts. Enclave members/contributors would enjoy routine access to the data and would share in any royalties from products developed from it.

How It Could Work

Imagine a physician, faced with a patient with advanced cancer, who is considering the use of a new PD1/PD-L1 inhibitor. The patient is negative for the biomarker (PD1); but the physician also knows that, though PD1 expression is correlated with tumor response, some patients who are marker-negative also respond. If the physician decided to prescribe the drug, the physician's staff might have to navigate prior-authorization requirements through the patient's insurer—a laborious, time-consuming process. (Some off-label uses of the drug may also incur much higher costs for the patient, including paying the full cost of the drug out of pocket.)

Now imagine precision-oncology informatics supporting value-based pricing agreements. The physician could consult a database or data enclave exploring the experience of patients with similar molecular and phenotypic characteristics (including age and comorbidities). Where possible, electronic medical records would support enrollment in appropriate clinical trials. If the evidence supported the decision to prescribe, the doctor and the patient would then discuss the potential risks and benefits and decide if treatment was warranted. There would likely be little, or no, pre-authorization required: the manufacturer would have already agreed to share financial risk based on predetermined patient outcomes' metrics that are routinely collected through oncology medical records and other linked-data sources.

If the patient responds—the parameters of which would be defined in advance, including sustained tumor control and/or improved quality of life—the insurer would pay the full cost. If the patient did not respond after a predetermined number of treatment cycles, the manufacturer would agree to sharply reduce the drug's cost, perhaps even rebating the full price. "Super-responses," such as remissions, could be eligible for premium payments from the insurer, split between the manufacturer and the provider.

Patient outcomes (positive and negative) could be seamlessly shared with the oncology community in real time, allowing other physicians and patients to learn from every treatment, informing the next treatment choice. Bayesian analytics would help refine this information, making follow-up choices more likely to result in positive outcomes, thereby avoiding futile treatments.

As we aggregate the experience of hundreds, or thousands, of other physicians and patients with similar treatment profiles in data enclaves, researchers and manufacturers should be able to construct robust patient profiles that correlate molecular and phenotypic data with real-world outcomes. In short, the database itself becomes a tool for developing new precision-prescription protocols that expand far beyond the evidence included with the FDA-approved label and that support the ongoing evolution of nuanced pricing agreements.

Technology Assessment: Standard of Care, Generics, and Biosimilars

The business case for precision oncology is not limited to new drugs; it also includes the ability to rapidly compare outcomes against the standard of care, generic or biosimilar options, or repurposed medicines. In such an environment, drug-development strategies will likely change, too. Providers and innovators will collaborate to identify products with the most value in a given clinical setting or select cohorts of patients likely to benefit. Collaborations will likely focus on cohorts of high-cost refractory patients, helping innovators focus their development efforts on candidate compounds that are most likely to deliver clinical and commercial success—including in earlier treatment settings—for themselves and for providers, who, increasingly, operate under their own value-based or capitated contracts.

As precision oncology advances, oncology drug-development failure rates would shift, allowing companies to weed out more compounds in early-stage testing or trials, with compounds entering clinical development being much more likely to succeed (and demonstrate substantial clinical improvements), thereby allowing industry to recoup profits from a larger number of approved therapies. At the same time, the collection of real-world outcomes data should allow for rapid label expansion. Today, supplemental new drug applications can take years and millions of dollars to complete. Informatics should allow providers, regulators, and innovators to reach agreement on observational clinical-trial designs in real-world settings that can produce high-quality data that substantially reduce the cost and time required to support a new label indication.⁶⁴

Under such conditions, would we spend less on cancer treatments overall? Payers' total spending on cancer medicines would probably rise; but indiscriminate, low-value, and futile prescribing would be reduced, and the value of insurance would rise because it would deliver better outcomes and more prolonged remissions to patients.

Rather than spend \$100,000 on ten patients (only three of whom might respond), pharmacy benefit managers and payers might spend \$50,000 or \$25,000 on 30 patients, with response rates much higher and more durable. Importantly, precision-oncology databases will allow us to identify savings from other parts of the health care system, too. Net prices paid by payers—inclusive of all costs and cost-savings—per patient should fall, resulting in more attractive net cost-effectiveness ratios. Most important, we will be saving and extending the lives of many more patients with serious cancers.

III. How Conditional Approvals for Precision Oncology Can Support Outcomes-Based Reimbursement

FDA regulators should be congratulated for increasingly shifting oncology drug approvals toward surrogate endpoints and molecular biomarkers that allow rapid market access after demonstrating efficacy in early-stage (Phase I and II) trials, as in the Breakthrough Therapy designation. They should also be lauded for embracing new, adaptive trial designs like I-SPY, BATTLE, and the Lung-MAP.⁶⁵ The FDA's oncology division is widely recognized as one of the agency's most flexible and innovative.

The problem: we will have to use treatment combinations for maximum effect on cancer; current clinical-trial designs are still extraordinarily time-consuming and expensive, and they enroll only a fraction of cancer patients because of restrictive inclusion and exclusion criteria.

In fact, it is not possible to efficiently test all the relevant compounds that we are likely to need to radically improve cancer outcomes through the traditional (sequential Phase I, II, III) clinical-trial framework for demonstrating drug safety and efficacy (i.e., where one drug is compared with the standard of care in a randomized controlled trial—especially when the standard of care is changing rapidly and when cancer-patient response to treatment varies dramatically). As Tenenbaum and Shrager noted in 2011:

Large-scale clinical trials are problematic in genomic diseases like cancer because they rely on population statistics rather than individual responses. A drug that works on 50 percent of patients tested may or may not be better for any given patient than one that works on 20 percent. This inability to account for individual responses may explain why so many late-stage [cancer] trials fail to demonstrate statistical efficacy, even though a few individuals do respond. What disease did these responders have, that used to be called “breast cancer” or “melanoma,” for which there is now an effective drug? How many other cancer patients have the same genomic disease? Unfortunately, we'll never know because when a trial fails, the drug is, as a rule, abandoned.⁶⁶

Tenenbaum and Shrager add that, because successful treatments will “often have to be used together in cocktails to ensure a durable response, there simply isn't enough time, money, patients, or specimens to test treatments individually on large heterogeneous patient populations.”⁶⁷ Such trials can take years just to accrue enough patients. By the time the trials are complete, the results may be outdated or affected by other drugs approved in the meantime. A better strategy: utilize “the complete molecular and clinical profile of every patient to efficiently decide which drugs are likely to work best in a specific patient.”⁶⁸ Vincent DeVita advocates this approach in *The Death of Cancer*:

Modern approaches to developing clinical trials require flexibility and the ability to adjust protocols on the run.... Most important is the fact that far more expertise exists at cancer centers than at the NCI and the FDA combined. Today we have the tail wagging the dog. And as a result, we are depriving cancer patients of what they—and their families—want most. A chance. We are losing too many people who should not be lost.⁶⁹

Frustration with the current “gold standard” clinical-trial system is reflected in the “Right to Try” movement, which advocates for state-based legislation that would allow terminally ill patients to access experimental medicines after Phase I trials if the manufacturer agrees to grant access. Right to Try⁷⁰ legislation has already been passed in 27 states and is a powerful statement that patients want more control of their medical choices when faced with a terminal illness. Industry, regulators, and researchers, however, are concerned that allowing access to unproven medicines outside clinical trials could compromise the quality of patient care and could even slow our ability to identify and advance more effective cancer treatments.

One approach that could expand access for patients without effective treatment options, while maintaining experimental rigor, is a conditional-approval pathway for oncology medicines. This paradigm would rely on expert oncologists learning to use candidate compounds in targeted cohorts of patients; using precision diagnostic and bioinformatics platforms, oncologists would rapidly match patients with treatments that they are likely to respond to, based on patients’ molecular and phenotypic profiles.

Under this approach, compounds would be given conditional approval after demonstrating significant activity in early-stage trials—where through a variety of preclinical and clinical tests, they show ability to modulate molecular pathways (biomarkers) or surrogate endpoints that are implicated in tumor growth or proliferation in specific cohorts of patients or disease indications.

The compounds would then be made available through clinical-trial networks, like the Cancer Cooperative Groups, National Comprehensive Cancer Centers, or any participant with the bioinformatics platforms (EMRs, decision-support tools, and experience in running sophisticated clinical trials). This would rapidly put promising compounds in the hands of oncologists with the requisite expertise and the most experience in treating patients with these characteristics. This infrastructure would allow such oncologists to collect real-world outcomes data in a variety of settings (i.e., early- or late-stage disease) and treatment combinations that could be analyzed to validate the clinical effects predicted by the biomarkers or surrogates and then to develop precision-prescribing protocols.

If the candidate medicines failed to meet prespecified endpoints—in combination-treatment regimens or as single-arm therapy—the FDA would have the authority to expeditiously withdraw the medicines from market; yet sponsors could continue development through the traditional-approval pathway. If they met prespecified endpoints—based on trial designs ac-

cepted jointly by the sponsor, NCI, and FDA—they would be given full approval and could be marketed outside the network. Critically, not only could conditional approvals slash the time and cost needed to bring new treatment options to patients who have run out of options; they would generate vital data—often absent today—on how new medicines perform in real-world patients. Ideally, to encourage large oncology-patient registries and seamless integration of patients into Phase I studies, clinical trials should become standard of care for off-label treatments, too.

One new paradigm for this type of approach is the PrECISE consortium for prostate cancer (Project to Construct Computational Models to Improve Prostate Cancer Treatment, Care). Members include IBM Research, Technikon, Technical University of Darmstadt, Aachen University Hospital, ETH Zurich, University of Zurich, Baylor College of Medicine, Curie Institute, and AstridBio Technologies. The aim:

[t]o develop different algorithms that allow us to understand tumor heterogeneity, understand better why drugs work and don’t work, and come up with more effective therapies [and] in particular combination therapies... [and to] develop computational approaches that integrate genomic, epigenetic, transcriptomic, proteomic, and clinical information.... [Consortium members] will combine data from a patient cohort with publicly available omics datasets as well as information from scientific literature. Consortium members will use the computational models that they develop to investigate prostate cancer’s molecular mechanisms and to try to predict new targets for therapy. The models will also help researchers stratify patients based on clinically significant and insignificant disease leads, which should help minimize unnecessary surgeries and ultimately lower healthcare costs.⁷¹

Such collaborations enable oncologists to rapidly test and validate new treatment approaches across a variety of disease settings and patient cohorts, allowing far greater learning than traditional clinical-trial designs that offer only binary succeed/fail outcomes at high cost. Carefully constructed virtual networks could also “avoid unnecessary replication of either positive or negative experiments ... [and] maximize the amount of information obtained from every encounter,”⁷² thereby allowing every treatment to become “a probe that simultaneously treats the patient and provides an opportunity to validate and refine the models on which the treatment decisions are based.”⁷³

The only thing missing from this platform—which Congress could supply as part of Vice President Biden’s “cancer moonshot”—is a regulatory pathway for rapidly matching promising

cancer-drug candidates with patients most likely to respond in a data-rich environment. Indeed, numerous health care experts have advocated this type of approach for nearly a decade. In 2007, for instance, one such group, convened by the Institute of Medicine, coined the phrase “rapid-learning health care”; the same group proposed a process for continuously improving drug science using data collected by doctors in the course of treating patients, focusing on groups of patients not usually included in drug-approval clinical trials.⁷⁴

Patient access in such an environment blurs the line between experimental treatment and FDA approval; but we should recognize that the high incidence of off-label treatment in cancer has already blurred it substantially. The aforementioned approach merely makes a virtue of necessity and formalizes a conditional-approval process that would grant access to larger cohorts of patients in a structured way.

Researchers at MIT, who have done pioneering work on conditional approvals for drugs more generally, write that a conditional-approval pathway linked to postmarketing surveillance could have a “profound effect” on drug development by “allowing smaller development programs to achieve greater success.... [Development costs could be reduced by 90 percent and development time by 50 percent] if the threshold for initial approval were defined in terms of efficacy and fundamental safety ... [compared with traditional strategies,] requiring high-quality and transparent patient registries for independent safety monitoring would be a more informative and cost-effective approach.”⁷⁵

Payers Are Ready for Change and Are Open to Experiments with Outcomes-Based Payments

Steve Miller, president of Express Scripts, one of America’s largest pharmaceutical-benefits managers, has called for a new paradigm for paying for cancer medicines:

*Paying for performance of a therapy should align with the value that therapy delivers to each individual patient. This approach makes therapy more affordable and accessible for all patients. For an indication-based formulary to work, we have to work with pharmaceutical manufacturers and others in the industry to determine how well drugs work for each individual patient. Scientific advances—such as tumor testing, predictive analytics and pharmacogenomics—will help guide this discussion.*⁷⁶

Europe may be ahead of the U.S. in its use of risk-sharing and pay-for-performance contracts. The Italian Medicines Agency has struck deals with manufacturers “that set payment based on how well a patient responds to treatment; and, in some

cases where the medication fails to help, the drugmaker gives a full refund.”⁷⁷ Use of such contracts has accelerated as more cancer medicines gain regulatory approval through small, early-stage trials. To date, Italy has received about \$220 million in rebates for products that did not demonstrate efficacy, representing about 1 percent of overall drug spending.⁷⁸

Johnson & Johnson and the U.K. government agreed on an expanded patient-access program where Johnson & Johnson would reimburse the government when patients did not respond to Velcade (a targeted treatment for multiple myeloma). Merck KGaA has adopted a similar program for cetuximab (for metastatic colorectal cancer), where costs are rebated for patients who have not responded after six weeks of treatment. Pfizer has also agreed to a program where it provides the first cycle of its kidney cancer drug, sunitinib, for free.

Celgene has capped (the U.K.’s) National Health Service (NHS) costs for multiple myeloma patients who remain responsive to lenalidomide for two years or longer. Janssen has struck a deal for its hepatitis C drug, Olysio, where the NHS will pay only for patients who fully respond within the first 12 weeks of treatment. However, these agreements are not widespread, and they remain handicapped by their administrative complexity. For example, in the NHS, patient-level outcomes data aren’t routinely collected, and retrospective rebates may “conflict with many NHS financial flows.”⁷⁹

Promising examples are taking hold in America, too. UnitedHealthcare, one of the nation’s largest private insurers, agreed to cover the OncotypeDX test, which can predict which breast cancer patients are likely to benefit from follow-up chemotherapy. Patients with a negative result were expected to forgo therapy, delivering cost-savings to the company and to members (through lower premiums). UnitedHealthcare agreed to cover the cost of the test while collecting data on chemotherapy utilization and costs. If chemotherapy use did not fall, Genomic Health would agree to negotiate a lower price.

Express Scripts, UnitedHealthcare, Harvard Pilgrim, and Aetna, among others, have expressed a growing interest in indication or outcomes-based pricing, where pricing varies based on the drug’s performance. Consider Tarceva, which is prescribed for pancreatic and lung cancer. Median overall extended survival in lung cancer, compared with chemotherapy, is three and a half months; for pancreatic cancer, it is only two weeks, compared with a placebo. Because of this difference, Express Scripts wants to pay a lower price for Tarceva for pancreatic cancer patients than for lung cancer patients.⁸⁰

Outside oncology, pay-for-performance deals have been struck for drugs for multiple sclerosis, congestive heart failure, diabetes, and a new class of cholesterol-lowering medicines (PCSk9 inhibitors). Says Christopher Bradbury, senior vice president of Cigna: “Competitive drug prices are important, but equally so is ensuring that customers’ medications are actually working as, or better than, expected.... When pharmaceutical companies stand behind the performance of their drugs through these kinds of contracts, we can deliver the most value to Cigna’s customers and clients for the money they are spending.”⁸¹

Conditional approvals would be a valuable—if not critical—adjunct to outcomes-based agreements by allowing innovators to spread their development costs and risks over more products, accelerate patient access to more effective products sooner, and build evidence on real-world costs and outcomes that can be used to support outcomes-based contracts.



IV. The Future of Database-Driven Oncology and Outcomes-Based Payments

When we talk of the costs of cancer care, especially the costs of new medicines, we risk missing the underlying truth that the burdens of cancer—as with any disease—lie largely in labor costs (physician and nursing care, hospitals, and hospice beds) and forgone productivity (premature death and disability and the value of lost life-years), not the costs of the medicines per se (**Figure 5**). According to IMS Health, the U.S. spent about \$39 billion (not including manufacturer rebates) on cancer medicines in 2015.⁸² Some analysis suggests that the full economic burden of the disease may approach \$1 trillion annually.⁸³ Other estimates show that productivity costs, including imputed earning losses for caregivers, will exceed \$300 billion by 2020,⁸⁴ with total economic losses due to shortened lives reaching nearly \$1.5 trillion.⁸⁵

Figure 5. Patients: Caught in the Cross-Fire

“Out-of-pocket expenses related to treatment are akin to physical toxicity, in that costs can diminish quality of life and impede delivery of the highest quality care.”⁸⁶

—Yousuf Zafar, M.D. and Amy Abernethy, M.D., Ph.D.

Understanding the burden of high treatment costs for patients is critical. High co-pays and coinsurance are associated with higher rates of prescription abandonment and delayed, or forgone, treatment, even when such treatments are highly effective. According to the New England Health Institute, high cost-sharing contributes to “medication non-adherence” and, in 2012, led to \$290 billion in avoidable health care costs.⁸⁷ Cancer patients under age 65 have higher rates of bankruptcy compared with patients without a cancer diagnosis: one study of colorectal cancer patients found that nearly 40 percent reported “at least one treatment-related financial hardship.”⁸⁸

Financial burdens on cancer patients appear to be growing. In a 2013 study⁸⁹ in *The Oncologist*, of 254 patients who sought assistance from a national co-payment assistance foundation:

- ◆ **75 percent** requested financial assistance for drug co-payments.
- ◆ **42 percent** reported “a significant or catastrophic subjective financial burden,” with nearly half (46 percent) cutting back on food and clothing spending—or relying on savings—to offset out-of-pocket health care costs.
- ◆ **Nearly 20 percent** “took less than the prescribed amount of medication” or “partially filled prescriptions”; **nearly 25 percent** “avoided filling prescriptions altogether.”⁹⁰

Today’s insurance system is not built for rapid-cycle, high impact innovations, especially considering that providers and insurers face their own significant financial stresses in the face of health care reform. Insurers may pay for a treatment today—as in the case of hepatitis C therapies, where treatments are not only cost-effective but likely cost-saving—yet the benefits largely accrue to future

payers, such as Medicare. Stakeholders must collaborate to develop better ways to encourage efficient oncology innovation and patient care in a system where cost growth is increasingly constrained and where more financial risks are being shifted to health care providers and patients.

In the long term, the incentives of manufacturers, insurers, and patients are aligned in the delivery of better treatments; but in the short term, volume-based reimbursement for new medicines (with fixed launch prices) leads to volume-based restrictions designed to deter the use of medicines in populations where they may be ineffective, or where evidence is still evolving. Silos for drug spending, hospital spending, and physician care also deter better care coordination, collaboration that can lead to better outcomes for patients for every dollar spent.

The business case for systematic reform to the oncology care system—and toward innovative pricing mechanisms for medicines—is undermined by an archaic payment system that predates the cell phone, let alone the Internet, electronic health records, and Big Data analytics. Unless we find ways to reduce the financial stress on cancer patients, faster regulatory approval may be a hollow outcome that leaves potentially effective treatments out of reach for too many patients.

Focusing on drug costs is understandable: drugs play a central role in the care of patients whose cancers cannot be tamed by surgery or radiation. The drugs that patients take are among the most routine part of their cancer care regimens, along with the co-pays or coinsurance that accompany them. Drug prices are much easier to parse than, say, an arcane hospital bill that most patients will never see. But focusing America's debate on only one component of cancer care risks neglecting broader discussions about how we can deliver better oncology care to patients for every dollar we spend—including the 75 percent of cancer costs beyond medicines. Widening our discussion to include all the risks, benefits, and costs of oncology care—including new incentives for delivering coordinated cancer care—will undoubtedly yield better outcomes than focusing on a single, albeit critical, component of that care.

Thankfully, such discussions are already occurring. Stakeholders across the oncology ecosystem—including Medicare, hospitals, drugmakers, private insurers, academic researchers, and FDA regulators—are already discussing ways to accelerate the pace of innovation; to make cancer care more efficient; and to reform payment systems. Innovative pharmaceutical companies, such as Eli Lilly, and insurers, such as Anthem, are asking Congress to reform outdated regulations that prevent insurers and companies from developing new value-based contracts that pay for medicines based on their effect on patients, based on real-world data.

The alternative to better market-based competition is more centralized government pricing. Other developed nations, including in the E.U., often will not cover new cancer medicines, even after regulatory approval, before they demonstrate comparative effectiveness compared with older drugs and/or meet certain cost-effectiveness criteria—such as costing less than \$50,000 per quality-adjusted life-year. U.S. proponents

of such measures argue that such constraints are necessary to control runaway health care spending by limiting access to only the most cost-effective therapies. Rationing, they argue, is the only rational response to manufacturers' pricing advantage derived from monopoly patents.

The problem with this logic is that it is extremely difficult, a priori, to know which cancer therapies will be of most value—not just after they are approved by regulators but one, five, or ten years later. A drug that seems to be an incremental improvement when it is approved, such as tamoxifen for breast cancer, may turn out to be a critical component in a drug combination tomorrow. (Tamoxifen, now a cheap generic, has evolved into a frontline treatment for women with locally treated breast cancer at risk of recurrence; tamoxifen reduces recurrence risk by 25 percent and reduces mortality risk by 30 percent,⁹¹ a discovery that was made after the drug lost patent protection.)

Requiring more comparative-effectiveness data prelaunch—or capping prices at an arbitrary level—imposes even greater drug-development costs and risks on innovators, thereby reducing the number of therapies reaching patients. Ironically, increased pricing regulation can reduce competition, keeping prices higher than they might otherwise be. While dialogues about evidence and value are still evolving, a number of promising initiatives can serve as stepping-stones for innovative stakeholder conversations about ways to better define value and encourage shared decision making with patients.

The American Society of Clinical Oncology has developed a value calculator that compares the net health benefit of new drugs, including side effects, with the standard of care, along with information on expected out-of-pocket costs.⁹² The National Comprehensive Cancer Network (NCCN) is developing an “evidence-blocks” program, currently limited to two

disease states: multiple myeloma and chronic myeloid leukemia. Evidence blocks are a remodeled version of traditional NCCN guidelines and are designed to be a simple, visually accessible matrix of key measures of value, including efficacy, toxicities, and strength of the evidence underlying the specific NCCN recommendations.

Peter Bach of Memorial Sloan Kettering has launched an online tool, Drug Abacus, that allows anyone to compare actual drug prices with their “appropriate” price based on numerous variables, including the value of a year of patient survival, survival advantage of the drug based on FDA-approval data, toxicity, and other variables (such as the therapy’s degree of innovation).

The challenge to these nascent efforts is that variation in formulary-benefit design and patient cost-sharing, in patients’ willingness to pay (based on income or other financial assets) or other preferences, and in the rapid pace of technological change makes it difficult, and unwise, to try to quantify value too rigidly (or only based on drug costs).

Retaining provider flexibility while providing enhanced incentives for coordinated, evidence-based care will likely be key to developing more effective, efficient oncology care. UnitedHealthcare has seen promising early results with a large oncology-reimbursement pilot that allows practices to choose their preferred drug regimen for breast, colon, or lung cancer, while replacing practices’ previous profit on the drug’s margin with an episode-based payment that covers previous fee-for-service payments for physician and hospital care, hospice management, and case management.⁹³ (Everything else continued to be paid for on a fee-for-service basis.)

By divorcing physicians’ profits from the initial cost of drug therapy, it was expected that drug costs would be lowered. In fact, drug costs rose sharply: practices spent 179 percent more on chemotherapy while overall costs fell by 34 percent. UnitedHealthcare is currently attempting to duplicate the finding; but this example suggests that allowing clinicians to vary their choice of chemotherapy in the context of episode-based payments for other physician services may provide financial incentives that reduce the use of hospital and radiology services.⁹⁴

Importantly, UnitedHealthcare has also launched a fast-track drug-approval program that verifies benefits coverage for injected chemotherapies that meet NCCN guidelines, thereby allowing for immediate-coverage approvals. Since launching the program in June 2015, UnitedHealthcare has processed 17,000 requests—of which about 70 percent were approved instantly—with only one appeal and only a 1 percent rejec-

tion rate.⁹⁵ The program is also “building a database that will enable UnitedHealthcare to analyze comparative effectiveness among different chemotherapy treatments for the same type of cancer; the company expects to publish the first comparative-effectiveness results in two years.”⁹⁶

We should encourage more of these experiments on platforms that are transparent to all stakeholders; we should also develop the infrastructure needed to make rapid advances in precision oncology. As such, stakeholders and policymakers should focus on the following:

1. Develop the IT systems, including data enclaves and patient registries, to better capture the full costs and benefits of different treatment and delivery approaches across a given disease state. This should allow payers, providers, and innovators to better evaluate the impact of innovative payment or delivery-system approaches on total costs and outcomes, as well as incentivize providers to seek the most cost-effective mix of treatment and prevention strategies, in the most cost-effective settings, without micro-managing patient and prescriber decision making.

We also need to aggregate large patient data sets that include structured and unstructured data that can be curated to provide useful Big Data platforms. Curation will allow us to turn data into analyzable information that allows clinicians to easily query the data using a wide variety of analytics. Federal payment policies—such as Medicare coverage of next-generation sequencing—should be carefully calibrated to promote responsible data-sharing. Data enclaves should be established that allow the democratization of data access, while also creating a business case for data-sharing through standardized licensing, royalty, or fee agreements.

Stakeholders need not start at ground zero for these efforts. Industry-led collaborations to share comparator-arm data, such as Project Datasphere, housed on a SAS analytic platform, are promising efforts to gather and share data that could provide templates for the trusted neutral ground needed to develop a core-oncology data set to guide real-world data collection and evaluation.

FDA regulators should also collaborate with stakeholders on the development of a core-oncology real-world data set and on standards for observational trial designs that could be used to advance validation of off-label treatments captured in data enclaves or trial networks. These standards could allow rapid repurposing of existing branded and generic medicines, further increasing market competition. As part of this effort, Congress should do much more to ensure that patients can control their

own data, including strengthening patients' right to view, transmit, and share their data with trusted intermediaries.

2. Accelerate regulatory reforms that lower the costs and risks associated with oncology drug development and encourage drug repurposing. Given the rapid entry of whole-genome sequencing and increasingly sophisticated bioinformatics platforms into the clinic, a system for oncology conditional approvals that enables faster access to biomarker or surrogate endpoint-guided medicines earlier in the development process (after baseline safety and efficacy have been established) should help oncologists and innovators identify effective compounds or combination therapies as early as possible—and significantly lower development costs and risks.

At MIT's NewDIGS initiative, insurers, providers, innovators, and FDA regulators have come together to help identify how a conditional-approval mechanism could accelerate access to new therapies after early-stage clinical testing in targeted populations. The NewDIGS model could be piloted through a coalition of willing cancer centers, patient groups, payers, and manufacturers.

3. Make a greater commitment to survey and incorporate patient preferences throughout the oncology care continuum. Value should ultimately be determined by the needs and preferences of cancer patients and their families. Rather than assume that we know what patients value, we must ask them. Patients might prefer less aggressive, less toxic approaches that preserve quality of life at the expense of living longer.

The patient's voice in regulatory decisions, drug development, and insurers' coverage decisions should be sharply amped up. Collecting better data on patient-reported outcomes—beginning with premarket clinical trials—can make it easier for patients and their physicians to identify treatment strategies that best align with their values and goals. Collecting patient-reported outcomes in the postmarket can help guide future drug-development and delivery-system reform strategies as well.

4. Embrace novel reimbursement strategies, but don't expect one size to fit all. Traditionally, co-pays and coinsurance were used to discourage the use of ineffective or marginally effective health care goods and services. But as outcomes-based contracts proliferate—and as the databases supporting shared decision making become more powerful—insurers should reduce these barriers to ensure that patients have access to highly effective therapies. Payers and innova-

tors can also agree to vary price based on how long a patient remains responsive or compliant with therapy, is in remission, has a disease that does not worsen, or develops fewer toxicities compared with standard of care.

We recognize that pay-for-performance strategies are apt to be much more data-intensive than standard payment models, especially when multiple manufacturers are involved in combination therapy, and not every payer, provider, or company can operate in this space effectively or quickly. But benefits from better outcomes, or reductions in ineffective treatments, are likely to offset these costs, and agreement on core oncology metrics for such contracts should reduce unnecessary variations.

Innovator companies may find it advantageous to consider novel revenue-sharing provisions when data suggest that combination treatments are much more effective than monotherapy—or to find other ways, such as via medical mortgages, to bundle effective treatments and services that reduce burdens on providers and patients. As former FDA deputy commissioner Scott Gottlieb notes, “[w]e are going to need to reconstruct how we pay for new technology to embrace the quickening pace that characterizes today's destructive innovation in medicine. To make sure that the resulting breakthroughs continue to reach patients requires us to have an approach to financing medical care that's as modern and imaginative as the drugs that are being invented.”⁹⁷

5. Create an FDA safe harbor for off-label prescribing. Companies may have access to data from clinical trials that are not included within a drug's FDA-approved label but would be of interest to insurers and clinicians to better understand the following: the product's rate of utilization; the benefits for specific cohorts of patients; and the impact on the utilization of other health care goods and services. Under current FDA guidelines, contracts that rely on off-label information could be considered impermissible off-label promotion, subject to fines and criminal enforcement.

These rules are being challenged by industry and have been designated as protected First Amendment speech in the Second Circuit.⁹⁸ This has left muddy waters for companies, and it would be far better and less time-consuming if the FDA issued a guidance to allow a safe harbor for such discussions, including the dissemination of any molecular and/or financial information that might be used to support development of outcomes-based reimbursement contracts among sophisticated payers, providers, and manufacturers.

6. Allow novel value-based contract designs to operate outside the Medicaid best-price construct.

Discounts linked to value-based arrangements can have a material impact on pricing formulas used for large government programs—such as Medicare and Medicaid—discouraging innovators from offering more significant concessions to private payers tied to outcomes. Medicaid’s “best-price” requirement, for instance, determines rebates partly based on the best price available to other payers. As Eli Lilly and Anthem note in a 2016 white paper: “[C]urrent Medicaid rebate regulations would require that rebates paid to a commercial health plan in the context of a single value-based contract be made available to Medicaid programs, even though Medicaid programs would not be subject to the key design features of the value-based arrangement.”⁹⁹

HHS should create a safe harbor for outcomes-based payment arrangements, perhaps as a pilot to determine how such efforts might affect government-pricing formulas. HHS should also explore standardizing Medicaid 1115 waivers for outcomes-based payments, which would allow state Medicaid programs and innovators to develop innovative pricing agreements. HHS already allows such agreements under the

Delivery System Reform Incentive Payment program. Standardized waivers would allow contracts that took account of potential downstream cost-savings, including reduced hospital utilization. This would give states greater negotiating flexibility with manufacturers, while liberating companies from government price controls. Specific state pricing agreements, however, should remain confidential to encourage competitive pricing.

7. Create a safe harbor from federal and state anti-kickback statutes.

Federal and state programs are designed to deter fraud, waste, and abuse by not allowing physicians or hospitals to “self-refer” patients to services for which they have a financial interest. For instance, providers are prohibited from “offering or receiving remuneration (broadly defined) to induce or reward referrals for items or services paid for by federal healthcare programs.”¹⁰⁰ This may implicate outcomes-based contracting. For instance, if an innovator firm offered not to charge a hospital for patients who did not respond to its therapy, it might be construed as an illicit inducement to provide that therapy to Medicare patients. Regulatory safe harbors from HHS should make it clear that value-based contracts have a safe harbor from these provisions.

V. Conclusion

Companies and researchers are making exceptional progress in the battle against cancer. Their achievement is a testament to the dedication, inventiveness, and courage of the many patients, doctors, companies, and regulators involved. Oncology financing can appear especially daunting in the near term; but there are parallels to be found in our efforts to contain HIV/AIDS.

New regulatory frameworks, improved science (including routine genotyping of HIV and phenotyping of patients), and better education and prevention programs have all helped transform HIV infection from a death sentence into a manageable chronic illness. Today, mortality for HIV/AIDS has plummeted by 85 percent, and survival for HIV+ patients approaches that of uninfected Americans. While highly effective anti-retroviral therapies for HIV/AIDS make up over 50 percent of treatment costs, such therapies nevertheless produced more than \$600 billion in economic value during 1996–2010.¹⁰¹

Similarly, the rise of precision-medicine databases and analytical tools that can tell doctors and patients how best to match a specific drug with a specific patient’s disease may well help solve the problem of drug-price sticker shock by enhancing competition and delivering better value to patients and payers. Ultimately, the U.S. patent and pricing system helps to support a virtuous cycle of investment in innovation; market-based pricing encourages investment, followed by drug prices plummeting after patents expire and cheap generic substitutes enter the market.

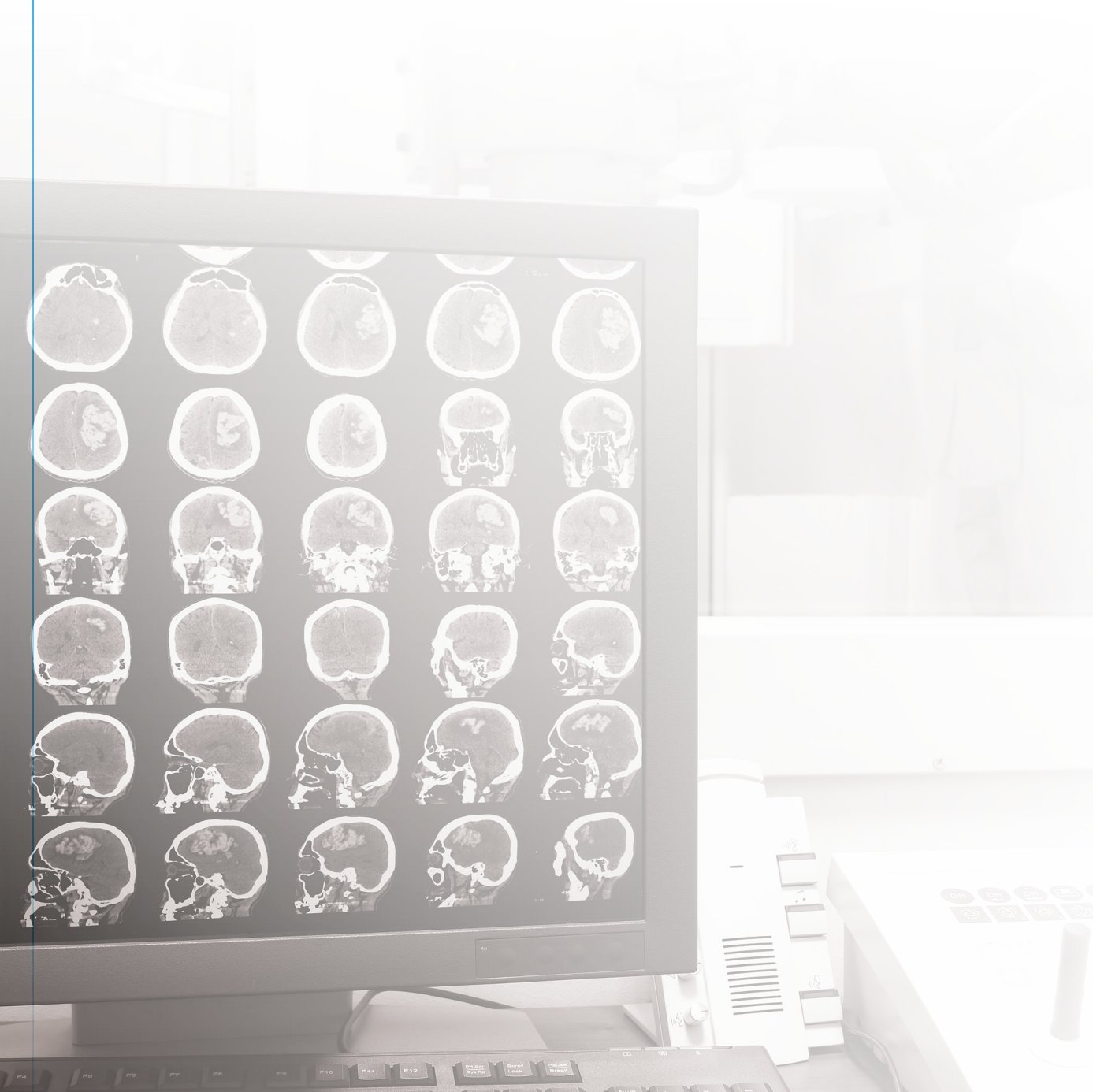
But for doctors to prescribe future generics well, they need access to the precision-medicine databases that are made possible by the innovators who launch patent medicines at premium prices. Insurers would also benefit from such databases, by allowing them to contract with provider networks that manage risk pools of high-cost cancer patients more effectively. As such databases and prescribing protocols improve, artificial-intelligence programs supporting precision oncology in the community setting offer opportunities to deliver high-quality care outside higher-cost hospital outpatient settings (where costs can be more

than 50 percent higher for metastatic colorectal cancer).¹⁰² Eventually, primary-care physicians could offer oncology care where care protocols are well established, lowering costs even further.

Innovation in American health care has sometimes appeared simply to raise costs without delivering better value to patients and payers. Technology assessment has often lagged new technology adoption, and reimbursement reforms are long overdue. Payers, however, must be cautious not to throw out the baby with the bathwater. As the economist James Robinson writes:

Innovation is a bond between the present and the future, a transfer of resources from today's society that finances research to tomorrow's society that benefits from new treatments. We need to purchase the technology of today with an eye on the technology of tomorrow.... The health care system has suffered from a deficit of effective purchasing, but this deficit is being overcome. Purchasing is becoming more sophisticated, cost-conscious, and value-based.¹⁰³

As a result, payers and providers are demanding more value from innovators. Building a framework for precision oncology and outcomes-based contracts can enable that value without slowing patient access to more effective treatment options. That is our national challenge—and an opportunity to be seized.



Endnotes

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Abstract

Companies and researchers are making exceptional progress in the battle against cancer. This paper makes the case for a new social contract for oncology drug development and reimbursement that can ensure that we accelerate the adoption of the right treatments to the right patients, while also experimenting with delivery-system reforms that may offer greater value to patients for every dollar spent on care.

Key Findings

- 1.** As access to high-quality oncology data and analytics improves, in real time and at the point of care, we have an opportunity to learn from every treatment decision and patient interaction so that we can improve outcomes and deliver better value across the entire cancer care ecosystem.
- 2.** Robust data-sharing of patient outcomes, combined with genomic and phenotypic data, can accelerate the advent of “precision oncology”—delivering the right treatment, at the right time, to the right patient; it can also serve as a platform for value-based reimbursement contracts that better align price with value by collecting data on critical metrics with much greater granularity.
- 3.** Regulatory reforms are needed to accelerate outcomes-based contracting, especially the creation of safe harbors from federal regulations governing “best price,” anti-kickback, and off-label prescribing.