

Cost vs. Value and the Price of Innovation in Cancer Care: Oral Anticancer Drugs in Multiple Myeloma, as a Case Study



March 28, 2018

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DISCLOSURES

- Dr. Fonseca has disclosed consulting with AMGEN, BMS, Celgene, Takeda, Bayer, Jansen, Novartis, Pharmacyclics, Sanofi, Kite, Juno, AbbVie, and Merck. He is a member of the Scientific Advisory Board of Adaptive Biotechnologies. Mayo Clinic and Dr. Fonseca hold a patent for the prognostication of myeloma via FISH, with an annual income of about \$2,000.
- Dr. Raj has disclosed consulting with Amgen, Novartis, Celgene, Takeda, and Janssen, and research funding from AstraZeneca.
- Dr. Hari has disclosed advisory roles with honoraria from Celgene, Takeda, BMS, Janssen, Spectrum, and Amgen, and research support from Celgene, Takeda, Spectrum, and Amgen.
- Dr. Usmani has disclosed consulting with Celgene, Takeda, Amgen, Janssen, Sanofi, and SkylineDx; speaker's fees for Amgen, Celgene, Janssen and Takeda; and research funding from Array Biopharma, BMS, Celgene, Janssen Oncology, Onyx/Amgen, Pharmacyclics, and Sanofi.
- Dr. Richardson has disclosed serving on advisory committees for and receiving research funding from Celgene, Takeda and BMS, and serving on Janssen advisory committee.

Executive Summary

As lawmakers at federal and state levels seek to address the issue of prescription drug costs, they too often do so without a general framework for evaluating the complex and competing proposals before them. Using multiple myeloma as an example, the authors of this paper—who include cancer doctors, cancer survivors, and an economist—lay out the economic, policy, and ethical considerations surrounding the issue of drug pricing and patient access. After examining issues surrounding value vs. cost, what payers and patients pay for drug treatments, and ethics and morality from the patient’s perspective, the authors propose that interference with market forces will stymie innovation and ultimately hurt patients.

Introduction

Great interest and controversy exist regarding the cost and affordability of cancer medications in the United States.⁽¹⁾ The topic has attracted the attention of physicians, patients, policymakers, and even the president of the United States. Individual physicians, physician groups, and medical societies have weighed in on the topic. The term “financial toxicity” is now common parlance in sessions at the American Society of Hematology and the American Society of Clinical Oncology (ASCO).^a

Few discuss how value should be defined and discussions about the merits of a particular treatment are uncommon. Therefore, we thought it would be worthwhile to examine the high cost of drugs from a multifaceted perspective.

This paper reflects an opinion from a group of concerned physicians, patient advocates, and health economists who worry that artificial interference with market forces (imperfect as they are) will lead to disruption of innovation and stymie the pace of research. In this paper, we consider unique economic and policy ideas but also look at the issue of cost vs. value from the most important perspective—that of the patient.

For discussion, we will use multiple myeloma, a bone marrow cancer that affects adults, as an example to illustrate the issues. Despite incontrovertible evidence that the survival of myeloma patients has greatly improved, most patients ultimately succumb to the disease, so clearly additional innovation is needed.^(2, 3) The current improvement in survival is due to advances in drug therapy with downstream cost implications.

This paper relates exclusively to the price of patented drugs and not generics.^b It is disingenuous to discuss the cost of patented and generic drugs as the same issue, though valid debate is needed about the transition of patented medications to generics. The economic considerations and implications of pricing and competition between generic and patented medications are fundamentally different and deserve different discussion forums. In a true market economy, unabated generic competition led by rapid approval and a sufficient number of competing producers should quickly result in optimal pricing.

So as we strive to achieve the best outcomes possible for myeloma patients, should we be talking about cost or value of these newer, patented drugs?

Economic considerations

Economic evaluations of drug pricing need to account for both costs and benefits. Sensational claims about price not only fail to advance an objective and scholarly discussion, they also fail to serve patient well-being.

VALUE VS. COST

At the heart of these discussions is whether the current pricing for newer drugs justifies their value. Absent formal pharmacoeconomic analysis (comprehensive economic analysis of a given medication), the question remains unanswered. However, it is incontrovertible that in the last 15 years we have seen dramatic improvements in the survival of myeloma patients, primarily because of the introduction of expensive new drugs.^(2, 3)

Cursory financial estimate analyses without the expected return on investment cannot accurately describe the tradeoffs between cost and value. If drugs improve the quality or quantity of life, there is an intrinsic economic value related to the additional time lived by individuals afflicted. For instance, if drugs can return a person to active economic activity, or decrease hospitalizations, transfusions, or surgery, there is an economic benefit to the individual, the payer, and arguably to society. Lower toxicity of newer therapies is of high benefit to patients' quality of life (e.g., lower neuropathy with lenalidomide), but assigning that a monetary value is difficult. Other imponderable benefits such as being able to see life-defining landmark events such as weddings or births are harder to quantify but worth noting.

Again, without a comprehensive analysis of such trade-offs, talking merely about cost is woefully insufficient. Economists routinely measure the economic value of years of life saved, and estimates can be made from extrapolations of survival gains. A full perspective, however, would evaluate both indirect as well as direct costs and benefits.

HOW MUCH DO DRUGS CONTRIBUTE TO RISING HEALTHCARE COSTS?

The rising cost of medications for cancer is often cited as the fastest-growing component of medical care, but as our studies have shown for myeloma, many other factors come into play, including increased utilization of inpatient and outpatient services.⁽³⁾

Drugs' contribution to healthcare expenditures has remained constant over the years. Drugs comprise 10 percent of all medical expenditures, while in cancer they comprise approximately 20 percent. And while the projected increase in spending is often portrayed using hypothetical scenarios that invoke the list value of medication, the numbers cited usually exceed the real-world experience. A recent study by Quintiles IMS, a human data science research and consulting firm, revealed that projected increases in drug spending were lower than previously claimed once rebates, or price discounts that are reimbursed back to the insurer were accounted for: 3.5 percent versus 9.2 percent in 2016.^c

Significant issues can affect affordability since co-pays are usually calculated based on the list prices. For a simple example, assume that a drug is listed at \$100. The patient has a co-pay of 20 percent. But the price after negotiated discounts and rebates is \$40. Had the co-pay been based on the negotiated price, the patient's portion would have been \$8 compared to the \$20 co-pay based on the list price. Again, expense without measuring the returns on expenditure is an incomplete analysis. Lastly, the analyses that examine rising drug costs do not take into account rising life expectancies among these diagnoses as a whole, despite evidence that pharmaceutical innovation is one of the primary drivers of increased life expectancies in recent decades.^d

STICKER SHOCK AND REBATES

When woven into physicians' conversations and publications examining expenses, the actual cost of medicines is presented in amounts that routinely exceed reality. The rhetoric assumes that patients pay average wholesale prices (AWP) and rarely includes estimated rebates, which are mandated discounts reimbursed to the insurer, for government programs such as 340B or Medicaid, an omission that unnecessarily increases sticker shock.^e Furthermore, to talk about a treatment "providing x months of survival advantage but at a yearly cost of y" without considering the duration of therapy is an incomplete argument.

Given the availability of the excellent biomarkers we have to monitor patients with myeloma, the treating physician can ascertain on a real-time basis through an iterative process the worth of therapy continuation. For instance, if treatment is given for one year and the patient responds during that time, then by extrapolation, a group of such individuals will derive greater benefit.

This group of similarly responding patients will be enriched for much better outcomes than the group at large. In other words, the return on investment is amplified when using monthly monitoring to decide on the continuation of therapy.^f

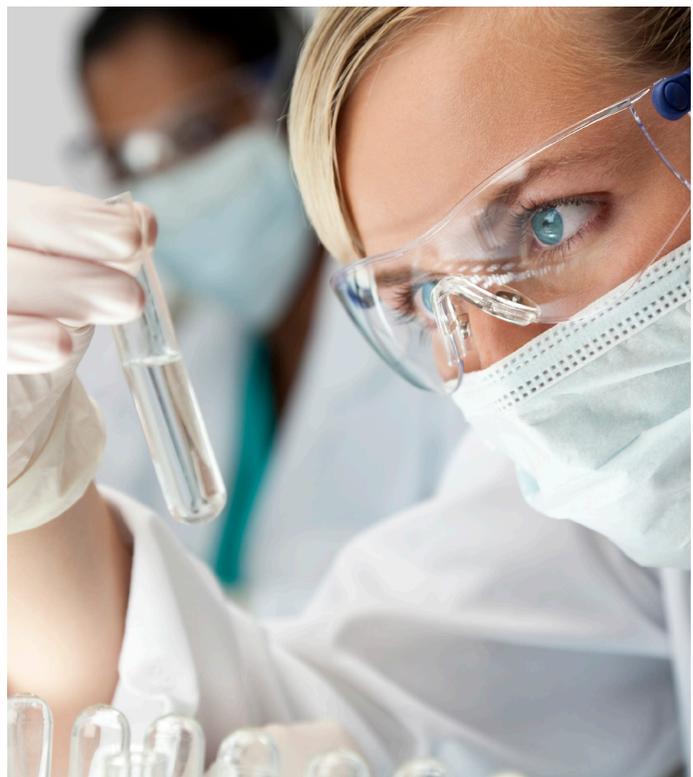
Today, science is beginning to allow us to see DNA sequences that, for example, are associated with multiple myeloma. We still have a paucity of predictive biomarkers, and they are important for the continued development of new treatments, including combination therapies. It would be interesting to approach biomarkers from both an economic and ethics perspective. For instance, the economic benefit may be infinitely positive for an individual with a predictive biomarker for the disease who also receives a successful combination therapy. In this case, there may be an even stronger ethical imperative to allow access to relevant drugs.

TRADE-OFFS AND RISK OF SLOWING RESEARCH DUE TO COST CONCERNS

One scenario that could result in the best long-term return on investment is to accelerate the drug approval process, thereby reducing the costs of bringing a drug treatment to market. Achieving cures or preventing chronicity of therapy in a meaningful fraction of patients would be desirable for all patients, even those who are not cured, and would yield enormous cost savings.

Long-term studies have shown that even when using older chemotherapy drugs with stem cell transplant, a small minority of cases can be cured. In one study, achieving a complete response was the best predictor of lack of progression at a follow-up of 20 years, a functional cure. (4) More recently, the same group has shown that the main predictor of long-term benefit is attaining MRD negativity.(5)

Ongoing clinical trials that test some of the most active drug combinations (e.g., regimens containing drugs used for myeloma such as



bortezomib, daratumumab, or carfilzomib, followed by stem cell transplant) show a very high rate of complete responses or MRD negativity. Halting, altering, or slowing clinical trials like these because of cost concerns is likely penny-wise and pound foolish.

VALUE OF OPTIONS

That is not to say that investing in therapies for relapsing myeloma is of limited value. In fact, the net value of subsequent lines of therapy is a composite of the net time of disease control plus the capacity of a survivor to reach a landmark point where additional, novel therapeutic options exist or will have been developed over the time period—these so-called “value of options.” It can be argued that the net value of any therapy like this should be the summation of these two factors.

The advent of immunotherapy treatments, such as the application of modified immune cells like CAR-T^g, offers tremendous potential for extending patient survival. A newly diagnosed patient who can survive five years from diagnosis now is likely to see the refinements still needed for CAR-T cell or bispecific antibodies^h to become mainstream, and perhaps curative in some. A sequence of induction, transplant, maintenance, and two lines of relapse management (e.g., daratumumab plus Rd and KRD) is likely to allow most patients to have such longevity, even if based on today’s currently approved medications.

The best example of the value of options was the advent of highly active antiretroviral therapy (HAART) for HIV. Patients originally treated with AZT but who lived long enough to receive HAART are now leading normal lives. During the early days of the epidemic, AIDS-associated complications accounted for up to 30 percent of hospital admissions at some county hospitals, with special wards built for care. Imagine if cost concerns had stopped such progress.

WHO REALIZES THE BENEFITS OF PAYING FOR INNOVATION?

Given that healthcare coverage is not necessarily based on a lifelong relationship with a specific payer, there is a legitimate concern about a payer’s long-term benefit for treatments with downstream savings. In other words, the payer of an effective treatment may not see the downstream benefits of such intervention, as another payer realizes savings. (Ideally, patients would fully control their healthcare dollars. While HSA-type approaches mimic this, the healthcare system remains a third-party payment system.)

A counter-argument to this is that balanced reciprocity will ultimately occur as best medical practices become mainstream, and thus the crossover between different payers will ultimately be of global benefit. Also, it could be argued that given the current state of healthcare coverage, the beneficiaries of prior effective interventions are Medicare and, to a lesser extent, employers with self-insured plans. Few if any patients will become covered by Medicare and then at some point exit the system for alternate coverage. As such, this concern is of higher relevance for commercial insurers than for the Centers for Medicare and Medicaid Services (CMS).

Policy

Many of the current policy proposals are flawed and misguided. Rather than promote healthcare access, they will create scarcity and stymie innovation.

ZERO-SUM GAME AND “RATIONAL PRICES”

There is much debate about policy recommendations to help tackle the high cost of drugs. Unfortunately, many erroneously assume a central pool of money is out there somewhere, and that society will convene

to best decide how to spend these healthcare dollars. Given this implicit assumption, people propose to establish “rational prices.”(6)

A second assumption is that a group of experts from various disciplines can coalesce in determining the proper price for a drug—that intelligentsia knows best! Yet no one has credibly argued how this could be accomplished without disrupting current market forces, however imperfect they may be.

Arguments for arbitrarily setting so-called rational prices are further amplified by assertions that “rational prices” can be determined. For example, a price would be set that rewards investments in biotechnology and pharmaceuticals at a level reflecting a “just reward,” but not “profiteering.” Basic economic principles and history have repeatedly shown the failure of this approach.(7) From Nixon’s wage and price controls to “price gouging” restrictions during hurricanes, government efforts to establish prices give producers and consumers the wrong signals: When prices are set artificially low, producers stop production and consumers over-consume. Proposing “rational prices” is proposing price controls, a sure path to scarcity.(6)

MEDICARE NEGOTIATIONS

One common recommendation is that Medicare should be able to negotiate prices for drugs as the largest purchaser in the world. Medicare already delegates some of its drug purchasing to the regional entities that manage drug purchasing for sets of beneficiaries. So adding another central level of negotiation (price setting) is of no immediate discernible value.

An older study by the Congressional Budget Office and the CMS Office of the Actuaryⁱ have concluded that allowing Medicare to negotiate prices directly would not further enhance the average discount of 35 percent, which third-party purchasers already get. Directly “negotiating” with a payer such as Medicare is likely to lead to arbitrary price set points—indirectly it is akin to price controls.

If Medicare negotiations were to start with a limited budget for total drug spending, rationing would be necessary. Rationing would most likely come in the form of Medicare non-inclusion of lifesaving drugs in a formulary. The situation would be similar to what is seen with the formulary of the Veterans Administration (VA) health system.(8) The VA formulary does not include some of the newer drugs, drugs that have been proven to be medically effective, and for which no adequate substitute exists.(8)

THE FAULT OF QALY-BASED PRICING PARADIGMS

Many paradigms of price negotiation or rationing for cancer therapies have at their flawed core assumptions and faulty applications of pharmacoeconomic evaluation techniques. At particular fault is reliance on the QALY, or Quality Adjusted Life Year.

The nuances and application of this metric should interest patients, physicians, economists, and policymakers alike. The Affordable Care Act, for instance, prohibits “adjusted life year (or such a similar measure) as a threshold to determine coverage, reimbursement, or incentive programs.” The VA has recently announced its intent to work with a group that uses QALY-based evaluations, and patient groups representing individuals with cancer and other diseases and disabilities have increasingly voiced concerns about this measure. QALY-based thresholds are explicitly used in the United Kingdom as a decision-making factor for a drug’s inclusion on UK National Health Service formularies, and many cancer drugs do not make the cut, leading to a lack of availability of these drugs to UK cancer patients.

The QALY is a calculation of time and utility, seeking to combine into a single metric both time regarding the quantity of life and utility regarding the quality of life. Since its development in the 1970s, the QALY has been criticized on both scientific and ethical grounds.

A recent publication reviewing the QALY's limitations has identified “ethical, methodological, and disease-specific or contextual” issues that can become “exacerbated” in an era of personalized medicine.^j

QALYs pose a bioethics quandary by valuing the lives of the “healthy” over those of the “sick,” implying that a perfect state of health makes a person more valuable, and failing to take into account individual circumstances. Measuring a “person’s value” when the person is sick is a flawed quantification.

Methodologically, QALY comparisons are often based on cross-comparisons of disparate datasets from different populations without statistical adjustment for these differences. The measurement instruments used as a basis for the quality-of-life component of the QALY, such as the EQ-5D, also have shortcomings. These shortcomings may be compounded when rolled up into the QALY and compared, such as a limited focus on mental health, lack of measurement of sensory function, and no measurement of non-health or societal factors that have demonstrable importance to patients (e.g., returning to work or functioning in school).

With regard to cancer populations and subpopulations with particular tumor types, or even within disease states, the QALY's shortcomings become even more acute. That is because the EQ-5D has low sensitivity for change in health status among cancer patients, time trade-off economic techniques are problematic in evaluating end-of-life situations, and use of projected survey data from the general population mismatches perceptions of cancer patients and survivors themselves.^k

Patient perspective, ethics, and morality

Contrary to conventional wisdom, one should not assume drug co-pays are the lone culprit in increasing the risk of medically related bankruptcy. Almost all patients have access to needed treatments, even when it poses a major financial challenge.

COST VS. AFFORDABILITY

The high cost of drugs is of course of relevant to all stakeholders, but foremost to patients. A recent Kaiser Health Tracking Poll showed that a large majority of Americans thinks drugs are too expensive and something should be done about it.⁽⁹⁾ Yet the same poll also showed that the majority had no difficulty in accessing medications. This dissonance is likely related to the negative public perception of pharmaceutical companies (also shown in this poll) and perhaps partly due to the constant flow of negative public information about these companies and the high cost of drugs.

It is critically important to differentiate between the cost and the affordability of drugs. Affordability of medications can be defined as the financial capacity of patients to pay for their fractional contribution to their cost of medications.⁽¹⁰⁾ Likewise, affordability also needs to be addressed with regard to physician fees and hospital charges.

People often conflate the terms affordability and cost. Is affordability a major issue? For some individuals it certainly is, but understanding affordability is nuanced. It is also worth noting that insurers are pushing more of the costs to out-of-pocket. Even if there is no increase in the actual drug price, it often feels like it to patients.

AFFORDABILITY IN MYELOMA

So, how difficult is it for patients to gain access to myeloma drugs? A study by Diplomat Pharmacies, a specialty pharmacy that dispenses lenalidomide^l, has shown that the majority of patients spend less than \$100 per month in co-pays for this drug.⁽¹¹⁾ Co-pay assistance is currently provided to the majority of

patients with commercial insurance, such that the monthly co-pay of the vast majority of patients will not exceed \$25. For those who are uninsured, the drug can be provided for free on a compassionate basis by the manufacturer. Therefore, for these two groups, lenalidomide is accessible and affordable, though for some households a monthly charge of this magnitude is still substantial.(11)

A greater problem with affordability exists among Medicare beneficiaries. Because of current regulations, direct co-pay assistance from manufacturers is forbidden, and thus third-party patient assistance foundations are the only entities permitted to facilitate financial support to help Medicare patients overcome the co-pay affordability hurdle, which can be burdensome due to the benefit design structure of many Part D plans.

While there is an initial shock for patients when the unassisted co-pay is mentioned, subsequent efforts will usually secure co-pay assistance so that patients can access these medications. However, there is significant effort invested by patients, their families, and healthcare teams to obtain such support. Some cancer centers are employing multiple full-time staff members solely to assist patients in navigating financial aspects of care and to access such support mechanisms; this expenditure of staffing resources and time also has a cost to the healthcare system.



ETHICS OF CONSUMERISM PRESSURE, STEP-THERAPY, AND PRE-AUTHORIZATIONS TO LIMIT USAGE

While not only relevant to myeloma, preventing direct co-pay assistance for Medicare beneficiaries could be construed as an attempt at creating “consumerism” pressure to prevent overutilization of drugs.(8) Very persuasive arguments have been made by economists regarding the failures of cost sharing for medical expenses.(12)

This consumerism pressure expects patients to be better “shoppers” and thus entice physicians to use cheaper alternatives. But there is simply no cheaper equivalent drug to lenalidomide for the treatment of myeloma. We refer to this fallacy as the “blue and the red pill,” a true rarity in cancer therapeutics.(13)

While at first glance, lenalidomide could be considered sometimes unaffordable, once co-pay assistance is secured, most patients can receive treatment. In these authors’ experience, we have always been able to have a patient receive the prescribed lenalidomide when medically appropriate. Stories about patients having to sell their homes to afford drugs probably exist but are more of an exception than the rule.

Several medical publications and media articles paint the practice of third-party foundation support as somewhat nefarious(14, 15) yet still recognize that interference will only make it harder for seniors to access drugs in the current system. This benefit design is also highly problematic from an ethical perspective. The original intent for medical insurance products was to insulate individuals against financial risk for large expenditures associated with catastrophic illness. This social contract removes the worry of insolvency in the face of large medical expenses.

It is notable that bioethicists have not pointed out two things. First, introducing consumerism pressure at the time of a cancer diagnosis presents the real possibility of creating additional distress for patients who are highly vulnerable. The consequences of such decisions would only add to the emotional distress of a cancer diagnosis. Second, by introducing a third party, whether payer or society, into decisions about the best drugs to use, the prescribing physician will immediately abscond their fiduciary responsibility to patients. In other words, physicians in this scenario are actually undermining the trust placed on them by patients.

“Notwithstanding the very significant financial burden that a cancer diagnosis creates, only a minority of cancer patients declares bankruptcy.”

In myeloma and other cancers, strategies to incentivize the use of cheaper drugs first, via the so-called “step-therapy,” have also been used. Some of these strategies include payments to physicians when they use, cheaper drugs in closed systems.

These approaches can expose patients unnecessarily to less effective or more toxic therapies. In myeloma, it would be ethically dubious to ask physicians to prescribe thalidomide^m prior to lenalidomide, given the inferiority and more toxic nature of the former.

Lastly, to better monitor usage of more expensive medications, payers often resort to a process of detailed preauthorization before such medications can be dispensed. These barriers can lead to underutilization of good medications because of attrition and fatigue by those less willing to seek the newer drug approval.

As previously mentioned, physicians and pharmacists expend significant resources to get prior authorizations/preapprovals, which are sometimes still denied. Seemingly cheaper in the short term, cheaper drugs could be more expensive long-term due to economic loss, toxicity, or shorter survival.

CANCER-RELATED BANKRUPTCY

A common rationale used by those advocating government interventions to lower prices is the risk of bankruptcy associated with a cancer diagnosis.(16, 17) Again, for this topic, the discussion should be focused on affordability, not cost. Studies have shown that a cancer diagnosis doubles the risk for an individual to declare bankruptcy, and that a sizable fraction of bankruptcies in the U.S. is caused by illness.

Notwithstanding the very significant financial burden that a cancer diagnosis creates, only a minority of cancer patients declares bankruptcy. However, none of the studies addressing medical bankruptcy have directly shown that it is the expenses associated with drugs that lead to bankruptcy, and creating that direct link is not possible with available data.

A cancer diagnosis creates many additional financial challenges for patients and their families including time off work, missed work for caregivers, travel and meals for those who may be geographically far from specialist care, hospital and emergency room bills and co-pays, and other medical and general expenses. It is difficult to study this effect on bankruptcy across the world, particularly as not all countries have bankruptcy protection laws like those in the United States.

However, it should be noted that the proportion of patients declaring medical bankruptcy in Canada, a country with universal healthcare, is similar to that of the U.S.(17-19) It is thus impossible to definitively conclude that it is the cost of drugs, even as a driving factor, that pushes cancer patients into bankruptcy.

Ethics of physicians as gatekeepers of cost containment

The physician-patient relationship is considered a fiduciary one where the physician's sole responsibility is to provide the best advice to patients, and not to conflate the needs of other interests. It has been argued that physicians treating myeloma should involve themselves in social activism aimed at reducing chemotherapy costs.

Gatekeeping is not the role of the scientist or the physician in or within our current economic model of healthcare. The primary responsibility of physicians is to the patient in front of them and to provide that patient the most effective and safest form of therapy. It is this fidelity to the patient that is a necessary prerequisite to upholding patient autonomy, the bedrock principle of medical ethics.

Similarly, recommendations on therapy should reflect a balance between clinical efficacy and safety in meeting a specific patient's needs, rather than costs to society. Without such an approach, our efforts to cure will be held hostage to the specter of cost concerns. Of course, activism separate from the clinic is anyone's prerogative.

Medical guidelines and value frameworks

Medical guidelines that introduce cost considerations incur a risk of denying patients best, evidence-based medicine, available therapies.

Several groups have tried to tackle the issue of high cost of drugs by creating economic evaluations of the various treatment options available for the disease. These include tools that value cancer drugs at large (e.g., Abacus)ⁿ or those that are meant to be more disease specific. The latter include those being developed by ASCO^o, European Societies, the National Comprehensive Cancer Network (NCCN) and the Institute for Clinical Evaluation and Research (ICER)(20). Efforts are primarily aimed at creating economic frameworks upon which the value of the therapies could be gauged.

Among the most widely publicized of these frameworks, thus far has been the one proposed by ICER, the Institute for Clinical and Economic Review.(20) Regarding myeloma, the conclusions reached by ICER's evaluation are problematic and do not reflect a bona fide approach to understand best practices for the treatment of myeloma better. The ICER process was largely limited by the lack of myeloma experts in its panels, the lack of meaningful input by key stakeholders, the lack of consideration of biologic variability among myeloma cases, and the fact that by the time of this writing, its conclusions are already outdated given the rapid pace of clinical research in myeloma.(21, 22)

Any myeloma expert will quickly recognize that the fact ICER holds in best esteem panobinostat (one drug recently approved for the treatment of myeloma but with major toxicity problems) needs to look no further for the limitations of such report. ICER has released reports evaluating other tumor types and interventions as well and has been met with similar criticism and skepticism by leading oncologists, for example in its evaluation of the emerging anti-PD1 and anti-PDL1 therapies for non-small cell lung cancer.^P

Similar to the criticisms noted above, these lung cancer thought leaders have stated that ICER's process is not peer-reviewed to a scientific standard, does not include disease experts as evaluators or authors, does not use patient-centered endpoints or definitions of value, does not reflect current standards of evaluation for evidence-based medicine, and lacks a mechanism for continuous review and revision. ASCO does not have a comprehensive guideline that addresses these concerns, so it cannot correct some of the deficiencies above.



The best available evidence for optimal clinical care comes from the NCCN Guidelines and Mayo's mSMART algorithm. These guidelines are primarily driven to select the best available therapy for myeloma patients, based on emerging clinical trial data and generated by evidence and expert consensus; however, they are not designed to address value.

International disparities

Patients in the U.S. pay a higher price for drugs than the rest of the world but often have earlier access to these medications, a consequence of the contribution to drug development by the U.S. private sector.

New drugs, no matter how desirable their therapeutic benefits, are not a right, and not for others to arbitrarily exercise intellectual property rights over. National and international laws that govern intellectual property exist to provide protection and return on investment for innovation.

Statements about disparities in access to newer anticancer drugs are usually framed in two ways. First, that the drugs are expensive and cost more in the U.S. than in the rest of the world. Second, that their cost makes them inaccessible to the rest of the world.

These two sentences simplify the complexity of the disparities, as there is a gradient on both costs and access around the globe. For instance, many nations with comparable GDP to the United States probably should pay prices comparable to those in the U.S. for access to innovative drugs.

DRUGS COST MORE IN THE U.S.

Nevertheless, both disparity statements are true—so what does this mean? First of all, newer drugs are usually more expensive in the U.S. market, while at the same time the United States disproportionately funds the largest share of drug development in the world.⁽²³⁾ Even when the net contribution of taxpayer dollars is substantial, if difficult to measure, the private sector incurs many more expenses needed to bring a drug to market and to sustain its use.

U.S. patients and payers face higher prices than the rest of the world for newer medications, but this premium comes with earlier access, sometimes measured in years rather than months.⁹ People often decry the lack of Medicare negotiations as a major driver of price and decry the poor negotiation skills of U.S. authorities. But it is important to remember that innovation will only be funded in areas where there is a significant return on investment.

The pharmaceutical and biotechnology sectors compose a significant portion of the larger market. A single-agent investor is unlikely to have any meaningful effect on the overall market forces behind innovation related to new drugs.

GLOBAL DISTRIBUTION OF REVENUE FROM NEW DRUGS

The net revenue from the sale of new drugs is the composite of the number of doses dispensed worldwide and the price per unit of dose over the time of patent protection. Given that many other countries are unlikely to pay U.S. AWP of drugs, pressure increases to raise the price of drugs in the U.S.

In other words, the current pricing in the U.S. subsidizes the cost of drugs for the rest of the world. And the sheer magnitude of the U.S. market is such that the proper pricing structure here is what dictates the financial success of the pharmaceutical sector. Foreign-based companies (e.g., Novo Nordisk) do not create innovations expecting local reward (few units and lower price per unit); rather, they aspire to have their return be based on the U.S. market.

Some have suggested that the duration of medication patents should be shortened. Mathematically, this would only enhance the desire for even higher prices to achieve an expected return within the shortened period of exclusivity.

The U.S. biopharma sector contributes substantially to the economy via employment, but also indirectly via scientific research and advancement, and medical education and grants to patient groups. These indirect contributions are either lacking or have to be explicitly supported by payers and government in other countries, which in the U.S. would come from taxpayer dollars rather than private funding.

INDIRECT GLOBAL BENEFITS

Two humanitarian arguments could be made in favor of the current system of higher prices in the U.S. and delayed global access: 1) The drugs one day will become the generics of the future and can be considered a gift to humanity. Perhaps these generics would have never been developed absent the possibility of a high return on investment in the U.S. 2) The early adoption of drugs in the U.S. allows clinicians to understand better post-approval experience, leading to better use. This post-approval experience will include better dosing and schedule, and an increased understanding of unique toxicities and the nuances of the drugs in combinations.

Fully understanding the optimal use of these drugs often requires an empirical, ongoing process of refinement post-approval. This experience will occur primarily in countries with early access.

COMPULSORY LICENSING

It is also true that even at discounted prices, some of these new drugs will be beyond the reach of citizens of other nations. Regrettably, this will be no different from other goods and commodities that are linked to the state of economic development of nations. However, a full pharmacoeconomic analysis should be created for each of these drugs, as they may appear to be expensive and, yet, their lack of use may be of greater economic expense.

Some analysis has shown that while the U.S. spends more on drugs, it spends less on cancer care than some European countries. It has also been suggested that global inequality can be reduced by improvements in healthcare, and thus reflexively dismissing drugs as beyond reach is not appropriate in all cases.

Nevertheless, poorer countries will still have impossibility of access, and new drugs will only become available when they become generics. Because of this inaccessibility, some countries have simply disregarded patent protections or have invoked compulsory licensing.⁽²⁴⁾ While the morality and philosophical principles behind this can be discussed, if the practice becomes widespread, it will further increase prices in the U.S. and ultimately stymie innovation.

The failure of public drug development

Public drug development may be an oft-cited proposal, but it is unlikely to work.

Many believe that the government should develop drugs as a public good, and thus provide them at a nominal cost. At first glance, this is an attractive idea but one that deserves empirical testing.

There have been no barriers or limitations for government-sponsored drug development, and yet the vast majority of drugs come from the private sector. Theoretically, it could be done, although it has not happened frequently. If governmental drug development were successful, we could all win through access at a lower cost, but the historical data would argue the likelihood of this happening is low.

An argument can be made that governments have the unfair advantage of using funds not tied to investor expectations and thus have an unfavorable competitive advantage. Or maybe it is a weakness? Perhaps drug development is not as easy as it seems. With the possible exception of bendamustine, all recent myeloma active drugs have been developed in free market economies by commercial enterprises.

A common argument is that because the government funds basic science research in academia, more reward should go directly back to the government. While universities do this type of basic research, they then patent and license the innovations to private sector companies, with a consequent financial benefit to the university, allowing them to further support research and education.

PATENT MONOPOLIES, COERCION, AND EMINENT DOMAIN

Another argument often made by those critical of drug prices is that drug patents create monopolies—of limited duration. Others have stated that patents are best described as periods of protected exclusivity.

Notwithstanding the fact they hold the actual patents, nothing prevents governments from engaging in nimble efforts to develop competitive products. (Was there a Sovaldi-like drug developed by the government?) For instance, a patent may exist for a drug or biologic such as daratumumab that protects the compound itself but not the target, but patents that protect specific targets are less common and rapidly vanishing. Why are there no more examples of parallel drug development by governmental agencies that could bring competition forward and prices down? No technical or scientific limitation precludes this. Perhaps then, commercial ventures are better conducted by the private sector.

Academic proposals have suggested that eminent domain should be invoked and drugs purchased at a price arbitrarily set by government.⁽²⁵⁾ Eminent domain laws were created to prevent situations where the owner of a land lot standing in the way of a railroad would not hold the government hostage and prevent completion of the project. Invoking eminent domain in the case of patented drugs seems more like designing a railroad that purposefully will go over gold mines and oil fields!

Conclusion

The process of medical innovation is slow, nuanced, unpredictable, and capricious. Despite attempts to create rational approaches for drug development, the empirical experience has shown that opportunistic gains can be as meaningful as those that come from hypothesis-driven goals.

In fact, it is the profit incentive that attracts investors to take the necessary, required risks associated with research, development, lengthy clinical trials, and long horizons for realizing gains, if any. If the goal is saving or improving lives, the worst thing government can do is remove or dampen profit incentives.

To further improve the care and survival of myeloma, additional investment is needed to develop tools that could cure a majority of patients. The answers of today are incomplete, and efforts to improve treatments must not be crippled, compromised, or even slowed down by concerns about the possible costs.

Is there a possibility in the future of a myeloma diagnosis where a short course of treatment could cure the disease? We can only hope so. But the only way to get there is to support the continued fervor of clinical trialists, drug developers, and investors. We owe it to our patients.

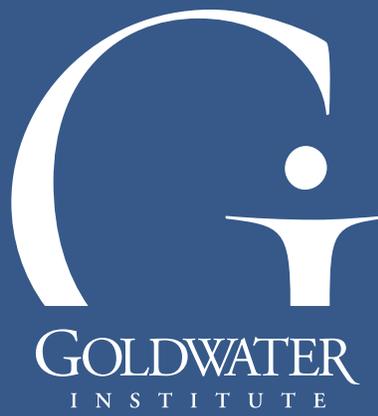
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ENDNOTES

- ^a http://www.asco.org/sites/new-www.asco.org/files/content-files/blog-release/documents/2017-ASCO-Position-Statement-Affordability-Cancer-Drugs.pdf?et_cid=39454952&et_rid=466246220&linkid=position+statement
- ^b A patented drug has received FDA approval and, as a result, can exclusively market and sell the brand-name drug for the duration of its patent protection. A generic drug is an equivalent to the patented brand-name product in dosage, strength, performance, etc. and can be sold once the brand-name drug's patent has expired.
- ^c <https://www.forbes.com/sites/matthewherper/2017/05/04/drug-prices-are-growing-at-the-slowest-rate-in-years-heres-why-it-doesnt-feel-that-way/#2ed5d740163e>
- ^d <http://www.nber.org/papers/w18552>
- ^e https://tumblr.co/Z0_1wo2N5wJ7Q
- ^f Exceptions exist, of course. Examples might include the monitoring of disease in the maintenance setting (potentially to be changed with the use of more sensitive monitoring tools such as MRD, or minimal residual disease monitoring), the use of immune-oncology drugs (drugs that target the patient immune system), or the use of combinations in the absence of biomarkers predicting response to each of the individual agents of such combination.
- ^g CAR-T cells are a novel way in which the patients' own immune cells are programmed to fight the cancer cells specifically, via a process of genetic engineering.
- ^h Bispecific antibodies, like CAR-T cells, are triggers for the patient's immune cells to fight myeloma cells.
- ⁱ <https://www.cms.gov/Newsroom/MediaReleaseDatabase/Press-releases/2007-Press-releases-items/2007-01-11.html>
- ^j <https://www.omicsonline.org/open-access/the-limitations-of-qaly-a-literature-review-2157-7633-1000334.pdf>
- ^k <https://www.ncbi.nlm.nih.gov/pubmed/21599035>
- ^l Lenalidomide is an oral medication frequently used in the treatment of myeloma. It is derived from thalidomide, its parent drug.
- ^m Thalidomide is a precursor to lenalidomide and a drug that can be used as treatment for myeloma. While it can work, it is thought to be less effective and more toxic than lenalidomide. It is available worldwide, and at a much discounted rate.
- ⁿ <https://drugpricinglab.org/tools/drug-abacus/>
- ^o <http://ascopubs.org/doi/full/10.1200/jco.2016.68.2518>
- ^p <https://obroncology.com/article/op-ed-our-view-on-value-frameworks-in-oncology-proposing-principles-for-value-framework-development/>
- ^q http://www.med.mcgill.ca/epidemiology/courses/EPIB654/Summer2010/Policy/Cancer_Report%20Karolinska.pdf



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