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REVIEW ARTICLE

Cost of Cancer Care: Issues and Implications

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A B S T R A C T

Medical technology is increasingly costly in most fields of clinical medicine. Oncology has not been spared from issues related to cost, in part resulting from the tremendous scientific progress that has lead to new tools for diagnosis, treatment, and follow-up of our patients. The increasing cost of health care in general (and cancer care in particular) raises complex questions related to its effects on our economy and the citizens of our society. This article reviews the macroeconomic principles and individual behaviors that govern medical spending, and examines how cost disproportionately affects various populations. Our overall goal is to frame debate about health policy concerns that influence the clinical practice of oncology.

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INTRODUCTION

Medical technology is increasingly costly in most fields of clinical medicine. Oncology has not been spared from issues related to cost, in part resulting from the tremendous scientific progress that has lead to new tools for diagnosis, treatment, and follow-up of our patients. It is likely that additional advances in molecular biology will continue to generate new opportunities for translation to the clinic. At the same time, we have vexing questions about the effects of treatment cost on our economy and the citizens of our society, many of whom lack access to high-quality cancer care. In this article, we attempt to inform debate about health policy concerns that influence the clinical practice of oncology.

WHAT ARE WE PAYING?

According to the Centers for Medicare and Medicaid Services (CMS), in 1965 approximately 5% of the United States gross domestic product (GDP) was spent on health care (Fig 1). Since that time, growth in health expenditures has consistently outpaced growth in GDP.In 2004, health expenditures were approximately 16% of GDP, and it is projected that by 2014 we will be spending nearly 20% of GDP on health care. The growth in the proportion of GDP devoted to health care reflects changes in intensity, volume, and costs of services provided to patients. Since 1965, there has also been a gradual increase in the proportion of national health expenditure that is financed through public sources. It is projected that almost half of health expenditures will be publicly financed by 2010 (these figures are underestimates because they do not include the tax expenditures related to health insurance costs to employers and employees).[1,2]

At a macro level, there is a question of efficiency of these expenditures for the public in the United States. When health expenditure figures are compared with those of other countries, it is clear that in the United States we are spending more per person and a greater proportion of GDP on health care than any other country; however, the value of this expenditure is questioned when life expectancy is not impacted by this aggregate level of spending (Table 1[3]; Fig 2[4]).

The National Institutes of Health estimated that the total cost of cancer care in the United States in 2005 was $209.9 billion.[5] Direct medical costs including inpatient and outpatient care, drugs, and devices accounted for $74 billion of this total, $17.5 billion was attributed to indirect morbidity costs (ie, lost productivity), and indirect mortality costs (ie, lost productivity due to premature death) accounted for $118.4 billion.[5] Given that cancer is largely a disease of older individuals, cancer expenditures will be of even greater concern in the future as the so-called baby boomer population swells the ranks of the US Medicare program from 42.5 million in 2005 to almost 70 million by 2030.[6] As evidence of this demographic trend (and as evidence of unmet clinical need in oncology relative to other disease contexts), cancer recently surpassed heart disease as the number one killer of Americans younger than 85 years.[7]

Much of the ire and angst expressed in the lay press regarding the cost of cancer care has focused on cancer drug treatment. Cytotoxic and biologic agents used in cancer treatment are among the

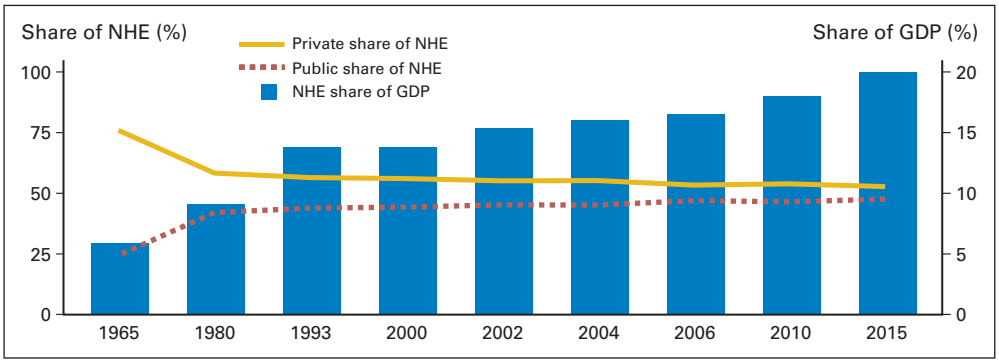

Fig 1. National health expenditures (NHE) share of gross domestic product (GDP). The left axis (public and private spending's share of NHE) relates to the two line graphs. The right axis (NHE share of GDP) relates to the gray-shaded bars. Data for 2006, 2010, and 2015 are projections. Reproduced with permission.[1]

costliest in medical care, and the unit cost of newer agents has shown substantial increase compared with older drugs. In some cases, these changes in costs reflect the increasingly tailored approach to cancer care that may limit the market size for some of these products compared with nononcology products.[8] In addition, initial approval of antineoplastics by the US Food and Drug Administration commonly is based on modest activity in patients with advanced metastatic disease. Thus, the traditional pathway for drug development may lead to initial licensing of treatments with relatively low apparent value. The maximal benefits of new antineoplastics may not be realized fully until years later when the results of adjuvant studies are available. In 2004, Medicare payments for all Part B drugs for medical oncology totalled $5.3 billion ($2.3 billion for chemotherapy and $1.5 billion for erythroid growth factors).[9,10] Furthermore, drugs prescribed by oncologists account for more than 40% of Medicare drug spending.[9,10] These figures exclude drug administration charges, evaluation and management services, and treatment of younger cancer patients not covered by Medicare.

Drugs used in the treatment of cancer patients account for a high percentage of medical drug expenditures in hospitals and outpatient clinics. As listed in Tables 2 and 3, cancer-related therapeutics represent a significant cost in both the inpatient and outpatient setting. Whereas inpatient use of cancer therapeutics is dominated by supportive care agents (ie, hematopoietic growth factors and antiemetics), anticancer treatments are among the highest expenses for drugs administered in outpatient clinics. When considering hospital spending on drugs, only anti-infectives and anticoagulants account for more aggregate cost than antineoplastics and blood growth factors.[11] It remains to be seen to what extent new high-priced oral antineoplastics will influence overall outpatient pharmacy expenditures.

The treatment of colorectal cancer provides an apt example of how new therapeutic advances can potentially influence the overall cost of care. Colorectal cancer is the second leading cause of cancer death in the United States.[12] Until 1996, only fluorouracil plus leucovorin (FU/LV) was available for the treatment of patients with colorectal cancer. The median survival of patients with metastatic disease was approximately 12 months.[13-16] During the last decade, three cytotoxics (capecitabine [an oral FU prodrug], irinotecan, and oxaliplatin) and three monoclonal antibodies (cetuximab, bevacizumab, and panitumumab) have been approved for use in the United States and other countries worldwide. Irinotecan, oxaliplatin, and bevacizumab have demonstrated a survival benefit when added to a FU/LV regimen. In each case, this benefit is measured in months. However, it is clear that the availability of multiple agents results in incremental improvements in survival that in aggregate are of value to patients.

For example, clinical trial populations that had access to fluoropyrimidines, irinotecan, and oxaliplatin had an overall survival of approximately 21 months.[17] It is anticipated that additional improvement in survival beyond 21 months will result from the availability of bevacizumab, cetuximab, and panitumumab. In first-line therapy of metastatic disease, bevacizumab improves survival when added to irinotecan plus FU by approximately 5 months.[18] Although a survival benefit has not yet been proven, cetuximab plus irinotecan has a 20% response rate and time to

Table 1. Life Expectancy and Health Expenditures Worldwide[3]

Country	Life Expectancy (female-years)	Total Expense per Person (US $)	% of GDP
Australia	83	2,519	9.5
Canada	83	2,669	9.9
Ireland	81	2,860	7.3
Japan	86	2,662	7.9
Monaco	85	4,587	9.7
Singapore	82	964	4.5
Spain	83	1,541	7.7
Switzerland	83	5,035	11.5
United Kingdom	81	2,428	8.0
United States	80	5,711	15.2

Abbreviation: GDP, gross domestic product.

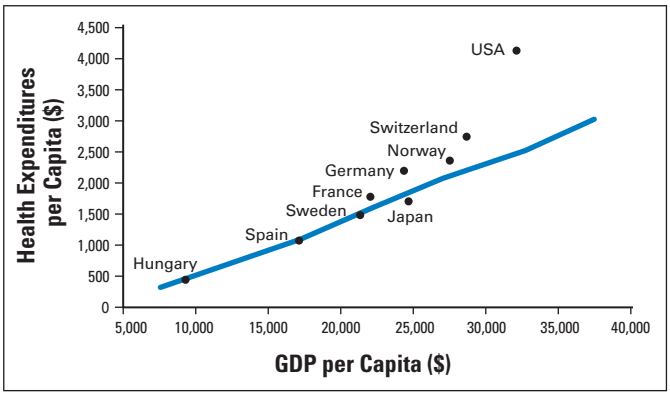

Fig 2. Health expenditures and gross domestic product (GDP) per capita worldwide. Reprinted with permission.[4]

Table 2. Top 15 Clinic Drug Expenditures[11]

Drug	Total 2004 Expenditures ($ in thousands)	Percentage of Total 2004 Clinic Expenditures
Epoetin alfa	3,901,126	17.7
Darbepoetin	1,214,297	5.5
Pegfilgrastim	1,160,429	5.3
Infliximab	1,269,004	5.8
Rituximab	950,981	4.3
Oxaliplatin	541,014	2.5
Docetaxel	635,990	2.9
Zoledronic acid	466,887	2.1
Trastuzumab	364,762	1.7
Gemcitabine	420,510	1.9
Paricalcitol	349,728	1.6
Pneumococcal vaccine, diphtherla conjugate	349,836	1.6
Irinotecan	327,023	1.5
Filgrastim	227,999	1.0
Carboplatin	317,603	1.4

progression of 4.1 months in patients who had previously shown irinotecan resistance.[19] Panitumumab improves time to progression compared with best supportive care by 46% in patients previously treated with cytotoxics.[20]

Table 4 provides cost estimates for commonly used regimens. The drug cost of FU/LV is less than $100 for a 6-month course. Commonly-used regimens that add irinotecan or oxaliplatin cost $20,000 to $30,000 for the same 6-month course. Bevacizumab contributes an additional $24,000, and the cost of weekly cetuximab alone exceeds $50,000. As shown in Figure 3, the aggregate drug cost for treatment of patients with metastatic colorectal cancer is $150,000 to $200,000 for an additional year of survival compared with FU/LV alone.[21] Ongoing studies will address whether a finite course of cetuximab or bevacizumab will improve the cure rate when administered in the adjuvant setting.

Table 3. Top 15 Hospital Drug Expenditures[11]

Drug	Total 2004 Expenditures ($ in thousands)	Percentage of Total 2004 Nonfederal Hospital Expenditures
Epoetin alfa	1,178,462	4.8
Enoxaparin	806,156	3.3
Darbepoetin	379,864	1.5
Pegfilgrastim	426,804	1.7
Infliximab	521,449	2.1
Ondansetron	497,174	2.0
Rituximab	451,023	1.8
Pipercillin-tazobactam	396,940	1.6
Propofol	470,571	1.9
Ceftriaxone	444,471	1.8
Filgrastim	335,413	1.4
Iohexol	344,644	1.4
Sevoflurane	267,090	1.1
Nesiritide	372,662	1.5
Eptifibatide	312,588	1.3

Table 4. Cost of Colorectal Cancer Treatment

Regimen	Cost per 6 Months ($)
FU/LV daily for 5 days, monthly	96
Infusional FU/LV every 2 weeks	352
Capecitabine for 14 days, every 3 weeks	11,648
Irinotecan every 3 weeks	30,100
Irinotecan weekly for 4 weeks, every 6 weeks	21,500
FOLFIRI every 2 weeks	23,572
FOLFOX every 2 weeks	29,989
Bevacizumab (alone) every 2 weeks	23,897
Cetuximab monotherapy weekly	52,131
Panitumumab	44,720

NOTE. Only drug costs included. Costs based upon average sales price for 70 kg patient with body surface area 1.7 m^2. Wholesale acquisition costs were used for panitumumab, as average sales price was not available at the time of publication. Abbreviations: FU, fluorouracil; LV, leucovorin; FOLFIRI, irinotecan, LV, and infusional fluorouracil for 46 hours; FOLFOX, oxaliplatin, LV, infusional FU for 46 hours.

Although efforts are underway to refine treatment algorithms based on predictive and prognostic markers, until success is achieved we may experience an explosion in multiagent and multimodality approaches based on the expanding availability of new interventions. This suggests that per-patient costs for therapeutics may continue to increase in the short to intermediate term, but perhaps moderate as more tailored approaches are validated.

HEALTH CARE AS DISCRETIONARY SPENDING

By using a relatively greater share of GDP for health care, relatively less of GDP remains to be spent in other ways. Fortunately, the United States is starting from a very high level of GDP, so we may have sufficient wealth to support high levels of spending on health as well as spending in other areas of the economy. Alternatively, our high levels of GDP may suggest that most essential goods are easily covered financially, and that we have more resources available to devote to the health sector. Economists view spending as choices by consumers. The invisible hand of the market is working when consumers perceive equal or greater value to expenditures than their costs. If we are all making choices to purchase more health care goods and services, then we are better off as a country with these choices. When consumers spend more of their discretionary dollars on health care, the economic implications are no different from those of any discretionary component of aggregate consumption. In other words, an economist might argue that it is our choice to spend money on health care rather than education or more plasma televisions.

From the standard economic perspective, consumers as individuals perceive different value from different mixes of goods and services. The strength of a free-market economy is the opportunity it offers individuals to maximize our own utility from spending by determining which products and services we want to buy. These choices involve trade offs between the costs and benefits of different alternatives to arrive at individual value propositions. We buy goods and services when we see more value in those goods and services than their costs.

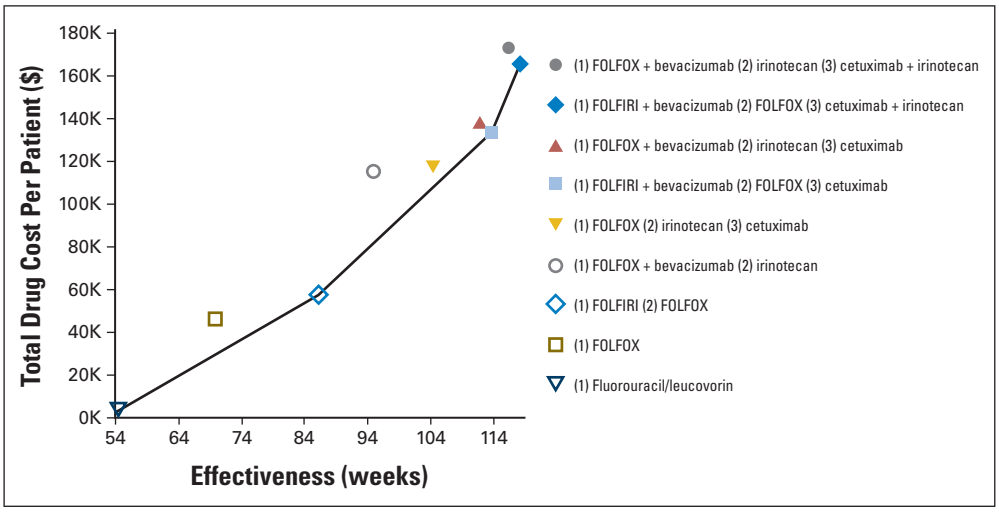

Fig 3. Cost effectiveness of colon cancer treatment. Reprinted with permission.[21] FOLFOX, oxaliplatin, leucovorin (LV) infusional fluorouracil (FU); FOLFIRI, LV, infusional FU, and irinotecan.

This basic analysis holds true for assessments of individual consumers spending their own resources on goods and services in the economy. However, health care spending is distinguished from other types of consumer activity by two key features. First, consumers often make choices not with their resources but with the resources of others, either through public or private third-party insurance programs. Second, health care spending has disproportionate burdens on different sectors of the economy because of the way health care is financed in this country.

WHY HEALTH CARE SPENDING IS DIFFERENT

Consumer Behavior

As individual consumers, we still make choices about spending for individual health care goods and services. However, we generally are not forced to make trade offs between the costs and benefits of alternative goods and services. In fact, many economists have argued that because individual consumers are largely protected from the costs of health care goods and services, value equations in health care are not based on considerations of the total cost of goods and services but on the portion of the costs borne by individual consumers, which represents only a fraction of the overall cost of health care spending.

Economists call this condition moral hazard: individual consumers purchase goods and services differently when they have insurance than when they do not, based on the differences in value decisions and costs under the two conditions. Because people with insurance perceive more than a dollar's worth of value for each out-of-pocket dollar spent, this leads to inefficient use and demand for perhaps unnecessary services. There is strong evidence that moral hazard exists, both from the RAND Health Insurance Experiment of the 1970s,[22] from more recent data on prescription drug expenditures and cost sharing,[23,24] and among insured and uninsured elderly patients.[25] This analysis would suggest that there is potentially an excess of spending on health care in the economy due to third-party payment as currently constructed.[26-29]

Extending this analysis to an assessment of cancer care is somewhat problematic. It is uncertain whether expenditures for cancer therapies are affected by the presence of insurance. However, it is clear that new cancer therapies such as those described are not affordable to most individual consumers in the absence of insurance.[30] One critical question is whether there is any evidence of moral hazard in cancer treatment decisions. One can imagine that as out-of-pocket expenses increase (eg, through copayment amounts), the demand for (ie, acceptance of) treatments with only modest benefits, or extrapolations of activity from one clinical setting to another in the face of limited direct evidence, will decline. Conversely, cancer probably represents a more insurable risk than other health conditions. Cancer is a catastrophic occurrence in terms of both its impact on health and its economic impact on patients. Fortunately, cancer is an infrequent event. Finally, the occurrence of cancer is not directly influenced by the individual in most cases, or at least there is a prolonged temporal lag between risk behaviors (eg, smoking) and the development of cancer. This suggests that an economic analysis of insurance for cancer therapies might result in less concern about the value of expenditures than an analysis of expenditures for other health care goods and services.

However, there are important caveats to this assertion. From an actuarial perspective, it is increasingly difficult to estimate the future costs associated with a new diagnosis of cancer, given the ongoing introduction of novel therapeutic agents at current price levels. In addition, as noted, the individual patient (and his or her physician) has some ability to influence the magnitude of expenditures associated with cancer treatment through choices of therapy once a diagnosis is made, especially in the case of supportive care, late-stage therapy, or use of brand-name agents versus generic equivalents.[31] Payment for oncology services has been criticized as providing a strong financial incentive to overtreatment of patients, rapid adoption of new brand-name products over generic versions of therapies, and to overuse of imaging services in the management of patients.[31-33]

The presence of insurance is not likely to be the only key influence on the medical decision making of cancer patients. In 2002, Daniel Kahneman won the Nobel prize in economics for his work on prospect theory with Amos Tversky—a conceptual basis for the field now known as behavioral economics.[34] The basic premise of prospect theory is that we make different decisions under conditions of gain and loss. Thus, a gambler who is loosing at the blackjack table may take increased risk to recoup his losses, whereas the same player may bet

more conservatively if currently winning. In our own research, we have applied prospect theory to the decision making of cancer patients who are considering treatment options. We hypothesized that cancer patients vary in the extent to which they have experienced a loss in their health, and acceptance of treatment risk is associated with the extent of this loss. Consistent with this hypothesis, in a study of cancer patients who had been offered participation in a phase I trial, we found that the likelihood of participation was correlated significantly with perceived loss of health, which was defined in terms of both quality and length of life.[35,36]

This application of prospect theory suggests that the demand for new medical therapies arises not solely from a neutral evaluation of the risks and benefits of therapy, but from considerations of whether there is hope of benefit from a treatment option, even under conditions of treatment risk and uncertainty about treatment benefits.[37] Prospect theory raises an entirely separate issue about funding for cancer therapies. It describes a condition in which patients may weigh risks and benefits of treatment differently than those healthy policymakers, physicians, and guideline panelists who define acceptable standards of care and treatment paradigms. In fact, cancer patients may appear to be risk seeking in making treatment choices. This does not imply that cancer patients are less rational beings, but rather apply a different decision-making calculus in weighing their options compared with otherwise healthy individuals. The definition of what is too expensive is in the eye of the beholder (ie, stakeholder).

Impact of Increasing Costs on Health Insurance

In the United States, we have relied on an employer-based system of health care benefits to finance medical goods and services. Although there are many problems with this financing model, it has been a relatively stable mechanism for some time. However, in an era of globalization of goods and services in the broader economy, the cost of health care has become a substantial cost of business for certain older US companies. Specifically, older firms have substantial obligations to retirees for health care benefits, obligations paid on an annual basis from current operations. US companies assert that they are no longer competitive compared with global or new domestic competitors who do not have the added fiscal responsibility of retiree health care benefits. For example, General Motors spent more than $5 billion on health care for its workers in 2005 and bears another $63 billion in health care liabilities for future retirees, while the market capitalization of the firm is only $18 billion.[38] In 2006, Ford Motor Company offered a buyout to 75,000 employees as part of a restructuring effort, in part driven by benefits costs.[39] Recent turmoil in the airline industry is also a reflection of differences in pension obligations between existing firms and new entrants into the market. As globalization continues to transform the industrial landscape, we may find that the cost of retiree health care obligations to private employers make them noncompetitive in the market and may even drive the companies into bankruptcy.[38] The incentive for some firms to choose different production techniques (eg, the use of relatively less labor) could exacerbate problems with the nation's aggregate ability to finance health care absent a major policy change.

These extreme examples highlight the pressure exerted by increasing health care costs on businesses. A common solution is cost-sharing (ie, increasing employee contributions to insurance premiums and selection of insurance plans with higher copayment amounts). Furthermore, higher insurance costs are passed to employees in the form of lower wages and lower salary increases.[40] Ultimately, increasing health care costs are associated with increasing numbers of uninsured or underinsured citizens, as more businesses are unable to provide this support for their employees, and more workers are unable to afford individual policies.[40,41]

Lack of insurance and underinsurance can influence the receipt of cancer treatment in several ways. As personal costs increase, underinsured or uninsured patients may be less likely to seek care, and hospitals are less likely to provide charity care.[42-44] Anecdotal reports of patients declining treatment because of high out-of-pocket expenses have recently appeared in the lay press.[45-47] Insurance companies and hospitals are also more likely to scrutinize the use of expensive interventions, erecting barriers to prescriptions, especially for off-label use. The Medicare Part D drug benefit allows tiered copayment structures for which patients pay a percentage of the total cost of certain high-cost agents up to the catastrophic limit.[48] The Medicare Part B drug benefit also requires a patient copayment on a percentage basis.[9] A survey by the General Accounting Office found that more than 30% of cancer treatment is off-label[49]; oncologists have historically had great flexibility in selecting treatments for their patients. Increasing costs are likely to result in challenges to this autonomy.

WHO SETS THE PRICE?

The direct costs of cancer care include diagnostic tests, hospital and physician fees, and the cost of drug therapy. As illustrated, the high price of new drugs obscures other direct costs that are more difficult to enumerate. The largest payer for health care in the United States is the government, and other public and private insurers tend to follow the lead of CMS in their coverage decisions. It is notable that CMS does not consider cost in these determinations. Rather, Medicare's mandate is defined in the 1965 statute that created the program: "Notwithstanding any other provision of this title, no payment may be made. . .for any expenses incurred for items or services which are not reasonable and necessary for the diagnosis of illness or injury. . . ."[50] Furthermore, a definition of "reasonable and necessary" did not accompany this or subsequent legislation. The barriers to development of such a definition as outlined by Tunis[51] include difficulty in gaining consensus among stakeholders; discomfort with the notion of taking decision making out of the hands of patient and physician; and negative impact on innovation in pharmaceutical, biotechnology, and medical device industries.

The costs of drug development include the costs of preclinical and clinical research, the costs of successful and unsuccessful research efforts, and the capital costs arising from the substantial investment required to fund all of these efforts well in advance of a product launch. Adams and Brantner[52] recently estimated the cost of bringing a new cancer drug to market, including preclinical and clinical testing, at approximately $1 billion.

This estimate for cancer drugs exceeds the development cost of other therapeutics in part because of the length of time required to conduct phase III cancer clinical trials.[53] This development cost is often cited by pharmaceutical companies to justify pricing of new therapeutics. However, the cost of drug development is only one aspect of the larger economics of the biotechnology industry.[54] Clearly, in a private system, investors (pharmaceutical firms, biotechnology firms, or venture capital investors) must seek a positive return for shareholders from these risky investments in

research. As the technology and the marketplace get more complex, risk and price both increase for new therapies. The US Food and Drug Administration has implemented its Critical Path Initiative as an effort to increase the success of drug development efforts (with the potential benefit of reducing both the risk and cost of these investments).[10] Other influences on pricing include production costs, postmarketing research investment, pricing of comparable agents, novelty, market size,[54] as well as financial market expectations. Policymakers continue to grapple with means to determine an appropriate balance between fiduciary responsibility for public and private health care programs and incentives for investments in future health innovations.

It is notable that whereas CMS does not negotiate price with pharmaceutical companies, government payers in other countries do consider cost in coverage decisions and also negotiate price.[55] Disparate pricing of drugs worldwide has led some to assert that the United States is in essence subsidizing health care for citizens of other countries.[56] Certainly, one could argue that pricing freedom for drug manufacturers in the United States stimulates investment and hence innovation.

THE BIG PROBLEM: DISPARITIES IN CANCER CARE

Disparities in cancer care are the subject of increasing concern to the oncology community. Numerous studies have documented that individuals from lower socioeconomic groups and specific racial and ethnic minorities have greater cancer risk and worse cancer-related outcomes.[57] Disparities in care exist at many levels, including diagnosis, treatment, and outcomes.[58-61] The causes for these disparities are complex, and include economic, cultural, and social factors.[57,62]

In examining the cost of cancer care, we must also consider the potential for increasing costs to worsen disparities in care. According to the US Census Bureau, 15.9% of the population was uninsured in 2005. Among non-Hispanic whites, the uninsured rate is 11.3% compared with 19.6% among non-Hispanic blacks, and 32.7% among Hispanics.[63] Furthermore, the risk of uninsurance is highest among those in lower income brackets, thus disproportionately affecting those most in need. Even among individuals with insurance, higher financial burdens from copayments or coinsurance programs could lead to difficult choices for individual patients, and also influence the decisions of physicians and hospitals. The growth of patient access programs supported by the pharmaceutical industry is one response to this challenge, but it remains to be seen if the most vulnerable would be as likely to take advantage of these programs. Furthermore, the complexity of the delivery system in response to changing financial incentives for providers may also have a negative impact on these same groups of patients.

CONCLUSION

In conclusion, how much cost is too much cost? Up to this point, our economy has absorbed relatively comfortably the increasing spending on health care in general and cancer care in particular. However, the continued introduction of high-cost novel cancer therapeutics and diagnostics (and those in other areas of medicine), reflecting scientific progress and reward for innovation, is likely to exert increasing financial pressure on patients, oncologists, payers, businesses, and society. Thus, we may expect an increasing threat to our ability to ensure access and provide high-quality care to all patients. In this article we have explored some of the complexities that characterize the delicate balance between providing incentive for innovation and fiduciary responsibilities as health care payers. These topics are considered in detail throughout this special issue of the *Journal of Clinical Oncology*.[53,55,64-72] The oncology profession is poised to exert a positive influence on the economics of health care, through identification and implementation of best practices, and vigorous support of clinical research efforts that will define these practices and the interventions of tomorrow. Furthermore, it is our responsibility to gain a nuanced understanding of these issues such that we may be well-informed participants in policy discussions and decisions that affect the care we provide to our patients.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The authors indicated no potential conflicts of interest.

AUTHOR CONTRIBUTIONS

Manuscript writing: Neal J. Meropol, Kevin A. Schulman

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