



**Facing the rising cost of chemotherapy in an aging population:
Proposed reform of the drug approval process**


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Abstract

The emergence of new, effective therapeutic options has brought marked improvements in survival times and cure rates for many cancers. The cost of these advances, however, is staggering and has stretched thin the budget of the Centers for Medicare and Medicaid Services (CMS). In order to maintain its fiscal stability, CMS's cost containment measures (e.g. the Medicare Modernization Act of 2003) have shifted cost to providers and health care consumers rather than restrict the availability of drugs or services. Such measures, however, fail to contain cost as they do not address the underlying etiology of soaring health care cost: unfettered access to exorbitantly priced drugs.

I use the example of chemotherapy for colorectal cancer in the elderly to explore the cost of cancer care, and to demonstrate how current policies not only fail to contain cost, but also unintentionally increase the disparity between the wealthy who can afford optimal health care, and the average American senior who may be unable to afford state-of-the-art cancer care.

I propose that in our system with finite resources, we must accept that we cannot provide all possible care to everyone. If cost containment measures are to be successful and equitable, we must redefine quality care as excellent care for all, rather than all care for some. Cost-effectiveness, in addition to comparative clinical effectiveness, must become a focus of the drug approval process. Reforms such as the establishment of an Effectiveness Committee to review the clinical and cost-effectiveness of all new drugs, use of these data through a new "conditional" FDA approval system and incorporation of cost-effectiveness in CMS's reimbursement decisions, and a cost-sharing policy with the

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pharmaceutical industry for drugs receiving only conditional approval by the FDA would begin to slow the growth in the cost of care.

Although making cost-effectiveness a central consideration in drug approval and reimbursement decisions is likely to be unpopular, the American populace and its physicians are already quite dissatisfied with the extent to which they must shoulder the burden of the rising cost of medical care. Failure to act will only worsen this dissatisfaction, while allowing the growing divide between the care available to the wealthy and the care available to most Americans to widen.

Overview

During his tenure as director of the National Cancer Institute, cancer survivor Andrew von Eschenbach called for the elimination of “suffering and death from cancer by 2015”.¹ With his call to arms, Dr von Eschenbach acknowledged that cancer research has advanced far enough that a future where cancer inflicts little suffering on the American people might be possible in our lifetime. Also implicit in his call to end cancer suffering and death is the notion that cancer care must be available equally to all cancer patients. In the current American health care system, however, these two notions are at odds, resulting in an expensive system that provides phenomenal care to some, and inadequate or no care to many.

Modern chemotherapy is increasingly effective, lending support to the notion that we might meet Dr. von Eschenbach’s goal. However, modern chemotherapy is also expensive. In the case of metastatic colorectal cancer, median survival has quadrupled in the past decade from 6 to 9 months to upwards of 24 months with the availability of 4 new classes of anti-cancer drugs.² The cost of that therapy, however, has risen nearly 70 fold, from \$900 for six months of fluorouracil with leucovorin to \$63,000 for six months of the most commonly used chemotherapy regimen—oxaliplatin, fluorouracil, bevacizumab. These new drugs have been readily embraced by cancer patients and their physicians, who together strive to get the best possible treatment available for each individual cancer patient. With such a goal, little attention has been paid to the cost of the newly available drugs or to the ramifications of rising cost on the long term stability of the American health care system. Thus, though overall survival from cancer has improved to degree thought only a dream a few decades ago, without brakes on either the

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price or the use of these new agents, the cost of cancer care has stretched thin the budgets of publicly funded insurers.

These budget difficulties have put a system already plagued by disparities in health care delivery in further jeopardy, thus making it more difficult to reach the second portion of Dr. von Eschenbach's call: to provide care to all. Disparities in what cancer services are provided to racial/ethnic minorities and the poor are already widespread in the U.S.³ In fact, though death rates from lung, breast, and colorectal cancers are declining, the disparity in cancer death rates between whites and racial and ethnic minorities is on the rise.⁴ With the high cost of modern cancer therapy, the Centers for Medicare and Medicaid Services (CMS) who provides care for the neediest of Americans, has begun to look for ways to pay for care; if the Medicare Prescription Drug, Improvement, and Modernization Act (MMA) of 2003 is any indicator of future reforms, such cost-containment measures will shift cost from CMS to physician practices through decreased reimbursement and to patients through increasing co-payments for services rather than addressing the underlying cause of increasing cost. As a result, those less advantaged will be even less likely to get cancer care.

With continued focus on increasing the "ideal" therapy—the care that Dr. von Eschenbach believes may eliminate cancer suffering—and little attention to the plight of the publicly insured and the uninsured, it is likely that we may be able to eliminate suffering for wealthy Americans, while worsening the burden of cancer on those less fortunate.

In these pages I will discuss why I believe that in order to diminish suffering from cancer, as a nation we must work together to redefine optimal quality health care. Rather

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than valuing only care that maximizes anticancer benefit at a hefty price, we must also learn to value cancer therapies that, though perhaps slightly less effective, are priced to allow all Americans with cancer to have access to treatment. Using the case of colorectal cancer in the elderly to illustrate my point, I will argue that our current policies and practice, predicated on the notion that we ought to provide ideal care to each individual, increase the use and cost of cancer therapy; because of a limited budget these practices are at odds with equitable health care delivery; past cost-containment efforts that maintain the ideal care paradigm, failed to control cost and risk worsening the equity of cancer care; and, future reform efforts ought to strive to achieve good care for all rather than ideal care for some. Finally, I will recommend that we begin this restructuring by reforming the manner in which we introduce novel anti-cancer therapies.

Ideal care, the current goal of the American health system

In her discussion of quality assessment, Gail Povar notes that the American health care system has generally adopted the notion that “ideal care”—meaning providing the best (most effective and least harmful) possible medical technologies for each individual—should be the standard by which we assess the quality of our health care.⁵ In our system striving to achieve ideal care for the individual, the primary goal of health care practice and policy is implicitly defined *a priori* to be to provide every patient with each treatment that has any chance of benefit, regardless of cost.

It is very important to note that Povar's argument that the highest quality of care is "ideal" care is not necessarily consonant with the Institute of Medicine's 1990 definition of quality of care as "the degree to which health services for individuals and populations

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increases the likelihood of desired health outcomes and is consistent with current professional knowledge". The IOM definition of quality is elastic enough to include the possibility that "ideal" care – if that means "all possible care" – may not always, or even often, be a "desired health outcome" for the patient, or for society as a whole. The nuance inherent in this definition notwithstanding, the provider and patient communities, in practice, appear to endorse the principle of "ideal care."

In the case of chemotherapy for cancer, this principle leads to our acceptance of exceedingly costly therapy for small, incremental improvements in cancer-free survival; to deny a patient such therapy, even if the incremental benefit over the standard of care option is small, would be to deny him or her the potential for a better cancer outcome, and thus would be in direct conflict with our *a priori* goal of maximizing care.

As we shall see in our discussion of chemotherapy use in older colon cancer patients, using "ideal care" as a paradigm for policy and practice decisions ultimately results in worse care, on the whole, for American cancer patients as it may preclude many from receiving any therapy because of cost constraints, a notion certainly antithetical to our common understanding of equity and fairness in health care delivery.

Rising costs of chemotherapy

Advances in drug therapy have been the most prominent and productive recent achievements in cancer care. Because of our desire to incorporate any agent or treatment with some benefit, most of the recently approved drugs have been rapidly incorporated into the therapeutic armamentarium of routine clinical oncology practice. And while a few drugs clearly have changed the face of a particular cancer diagnosis, many produce

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only small benefit, and a few are only non-inferior compared with the standard of care. The emerging field of molecularly targeted chemotherapeutics provides an number of illustrative examples of both our successes, drugs that may well be worth their price, and our failures, those drugs approved and used only because of our goal of providing each patient with ideal care at any cost.

Molecularly targeted drugs are designed specifically to attack the cellular alterations that cause and propagate cancer. Because they target aberrant activity, these drugs largely spare normal tissue from toxicity; thus, they are highly regarded as more effective and less toxic than standard chemotherapies. However, the cost of their development is staggering. Such drugs are the result of years of laboratory research into the molecular biology of cancer, and subsequent years of clinical testing in animals and humans to prove safety and efficacy, making the cost of developing a new cancer drug around a billion dollars.⁷ The pharmaceutical industry, that in combination with federal funding of basic laboratory research, foots the bill for drug development, has responded by marketing these agents at exorbitant prices: Bevacizumab (Avastin) is currently priced at approximately \$100,000 for a year of therapy.⁸

Bevacizumab is also an example of a drug that is effective, but perhaps over used in our quest for ideal care. Bevacizumab, a monoclonal antibody directed against vascular endothelial growth factor, was approved for use in metastatic colorectal cancer in combination with fluorouracil after a phase III, randomized control trial showed it prolongs time to cancer progression (the time the patient can remain on chemotherapy before their cancer grows) by a median of 4 months and prolongs overall survival time by a median of 5 months (Table 1).⁹ Patients treated with bevacizumab were also more

Table 1, Benefit of bevacizumab in metastatic CRC				
	IFL	IFL-bev	FOLFOX	FOLFOX-bev
Median OS	15.1 mo	20.3 mo	19.9* mo	21.3* mo
Median TTP	6.8 mo	10.6 mo	8.6 mo	9.4 mo
RR	37%	45%	50%	47%
IFL data from Hurwitz ⁹ , FOLFOX data from Saltz ¹⁰ . * OS combines FOLFOX and Cape/Ox arms, OS in FOLFOX subgroup not reported. Abbreviations: IFL, irinotecan, fluorouracil, leucovorin; bev, bevacizumab; FOLFOX, oxaliplatin, fluorouracil, leucovorin; OS, overall survival; TTP, time to progression; RR, response rate.				

likely to have their cancer shrink than those treated with chemotherapy alone, with response rates of 37% for chemotherapy and 45% for chemotherapy plus bevacizumab. At the time this study was designed,

the standard of care chemotherapy regimen was IFL (irinotecan, fluorouracil, leucovorin given by bolus infusion). Median survival in patients treated with IFL after their diagnosis of metastatic colorectal cancer was only 15 months, making a 5 month improvement with bevacizumab a marked improvement and reason for excitement. Yet, in a subsequent randomized controlled trial in which patients treated with the chemotherapy regimen that replaced IFL as the standard of care, FOLFOX (oxaliplatin with fluorouracil and leucovorin), were randomized to receive either bevacizumab or placebo, the benefit from bevacizumab was much smaller than in the prior study: a 0.8 month improvement in progression free survival, and no improvement in response rate.¹¹ Adding bevacizumab improved survival by 1.4 months compared with chemotherapy alone (Hazard ratio for death 0.89, 95% confidence interval 0.79-1.03), though the authors did not report on the benefit in the FOLFOX treated subgroup, rather they pooled patients treated with the standard of care (FOLFOX) with a newer, slightly less effective combination, the capecitabine/oxaliplatin regimen. Thus, with the current standard of

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care chemotherapy regimen, bevacizumab adds approximately one month of time on chemotherapy before cancer progresses, and an average of one month survival.

Given a price tag of approximately \$100,000 per year, the cost-effectiveness of bevacizumab has been questioned, particularly in Europe. Even when assessing cost-effectiveness of bevacizumab compared with the inferior chemotherapy, IFL, the incremental cost-effectiveness is approximately £47,000 per year of life gained and £63,000 per quality adjusted life year.¹² These figures would be much higher if cost-effectiveness were measured in comparison to the more effective chemotherapy, FOLFOX. Despite the newer evidence of only small benefit from bevacizumab, it continues to be used routinely in combination with FOLFOX as therapy of newly diagnosed metastatic colorectal cancer.

Another drug in routine use with marginal benefit is erlotinib (Tarceva). Erlotinib is a small molecule inhibitor of the epidermal growth factor receptor (EGFR), a growth factor receptor that is overexpressed on many common cancer cells and is associated with poor prognosis. Erlotinib was approved for use in metastatic pancreas cancer in combination with the standard of care, gemcitabine, after a randomized control trial found a 0.3 month (5.9 months versus 6.2 months) improvement in survival in patients treated with gemcitabine-erlotinib compared with gemcitabine alone (Hazard ratio for death 0.82, 95% CI 0.69-0.99). Patients receiving the combination were also slightly more likely to be alive at one year, 23% versus 17%.

An estimate of the cost of adding erlotinib to gemcitabine for metastatic pancreas cancer as done in this trial was estimated at approximately \$15,200 per patient, with an incremental cost effectiveness of \$410,000 per year of life saved and \$430,000 per

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quality adjusted life year.¹³ Though, appropriately this approval was not met with as much enthusiasm as was the approval of bevacizumab, this was the first trial to demonstrate a statistically significant improvement in survival over gemcitabine alone after years of failed trials. Likely because of this distinction, erlotinib is used in clinical practice for metastatic pancreas cancer.

Despite only marginal improvements offered by some drugs, others have drastically changed the prognosis of certain cancers. Imatinib (Gleevec) is one of these paradigm changing medications. Through its blockade of the Abelson tyrosine kinase, imatinib inhibits the underlying molecular abnormality that causes chronic myeloid leukemia (CML). With this oral drug, the vast majority of patients with newly diagnosed CML enter a prolonged remission. Imatinib is so effective that oncologists have had to rethink how to treat CML; in particular, the role of bone marrow transplantation—once the only hope for long term survival from this disease—is now uncertain. Imatinib does not come cheaply: one year's worth of therapy is estimated to cost approximately \$30,000,¹⁴ with an incremental cost effectiveness ratio compared to the prior standard of care of approximately \$43,000 per quality adjusted life year.¹⁵

Clearly, drug discovery has led to considerable advances in cancer care, but these have come with a marked increase in the cost of oncology services. Even in the case of a disease changing drug, imatinib, cost-effectiveness is still near the upper bounds of what is often considered to be cost-effective. With health care consuming a record approximately 15% of the U.S. gross domestic product in 2002, an increasing proportion of which is shouldered by public payers,¹⁶ the ability of the American health system to

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continue to fund unabated growth—a growth fueled by our desire to give each individual ideal care—is not at all certain.

Cancer in an aging population

The population of the western world is aging. In the United States, the number of people over 65 will double by the year 2030, at which point one in five Americans will be over 65.¹⁷ As the incidence of all of the most common cancers (e.g. lung, breast, prostate, colorectal) increases markedly with age, in the absence of a substantial increase in our ability to prevent cancer, this population aging will bring an increase in the incidence and prevalence of the nation's second-leading cause of death—cancer—and an increase in the number of elderly cancer patients. By 2030 an estimated 70% of cancer patients will be over 65.^{18, 19}

Recognizing that the face of the cancer patient is aging, most major cancer research organizations in the U.S. and Europe have developed geriatric oncology programs and research strategies to address better the needs of older cancer patients.²⁰ Thus far, research has focused on the extent of care currently offered to the older cancer patient and has largely found this care lacking. Notably, older patients are underrepresented in cancer clinical trials²¹ and are less likely than their younger peers to receive standard-of-care anticancer therapies such as chemotherapy or surgery.^{22, 23} These discrepancies in delivery of care between older and younger patients are perceived by many as underuse of effective therapy,²⁴ and the underuse argument appears to have garnered strong support from oncology thought leaders in the U.S. At the 2007 annual meeting of the American Society of Clinical Oncology, a leading international society of

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clinical cancer care, topics of geriatric oncology were more thoroughly represented than ever before.²⁰ The prevailing sentiment of the conference favored an increase in the use of anticancer treatment, particularly chemotherapy, in older patients.

Meanwhile, as we have already discussed, the pace and cost of new technology and drugs available to treat most common cancers has continued unabated. While I agree with the prevailing sentiment that age alone should not be a determining factor in the decision of whether or not to use chemotherapy,²⁵ and that there is a likely a good deal of undertreatment of eligible older patients with cancer, it is critical that we discuss how routinely treating a greater proportion of elderly patients than we do at present will affect the cost of cancer care in the U.S. I do not propose that maintaining a policy of undertreating older patients ought to be a cost-containment measure, rather suggest that the current climate that moves to promulgate our ideal care paradigm in older patients will further stress publicly funded health care, and that if we do not address this problem now, the consequences are likely to worsen the care for many Americans.

Colorectal cancer

Colorectal cancer is the second leading cause of cancer death in the United States. An estimated 150,000 Americans are diagnosed each year, approximately 66% of whom are over the age of 65.⁴ At the time of diagnosis 39% have localized cancer, 36% have cancer spread to regional nodes, and 19% have metastatic disease.⁴ Thus, at least half of all patients diagnosed with colorectal cancer are eligible, based on stage alone, for chemotherapy treatment. The majority of these patients are elderly.

Adjuvant chemotherapy for colorectal cancer is effective. In localized or regional cancers, in which the cancer is confined to the colon or the lymph nodes surrounding the colon, primary therapy consists of surgical removal of the cancer. However, in stage II and III cancers relapse rates range from 20-80% depending on the extent of the primary tumor and the number of lymph nodes involved at the time of surgery. Chemotherapy given post-operatively as an adjunctive therapy decreases the relative risk of cancer recurrence by 30% with 6 months of fluorouracil,²⁶ or by an additional 23% with 6 months of fluorouracil with oxaliplatin.^{26, 27} For example, a healthy 60 year old woman found to have a cancer invading through the wall of the colon and involving 6 lymph nodes has a 40% chance of being alive and cancer free at 5 years if treated with surgery alone. If given 6 months of adjuvant oxaliplatin and fluorouracil, her likelihood of disease-free survival at 5 years increases to approximately 70%. Given the small absolute reduction in the risk of cancer death afforded adjuvant therapy for stage II patients, estimated around 2-4%,²⁸ chemotherapy is considered optional in patients with stage II cancers and is strongly recommended for stage III, node positive, cancers

Chemotherapy in older patients with colorectal cancer

Proponents of expanding the use of adjuvant chemotherapy to the majority of older colorectal cancer patients have a sound platform from which to argue. Despite concerns that the elderly may be at risk for greater chemotherapy toxicity, older colorectal cancer patients appear to derive the same benefit from chemotherapy as do their younger peers and suffer little increase in toxicity. In pooled analyses of elderly patients (>70) treated on large, phase III clinical trials of both single agent²⁹ and

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combination chemotherapy regimens^{30, 31} for colorectal cancer, older and younger patients have an essentially equal likelihood of being alive and cancer free at 5 years. Older patients do have a slightly increased risk of suffering a treatment-related decline in white blood cell counts from chemotherapy,²⁵ but this does not appear to translate into an increased risk of severe infection.

Though older patients well enough to enroll on phase III clinical trials seemingly have little problem when treated in an identical fashion to younger patients, the majority of older patients diagnosed with stage II and III colon cancer are not as fit as those who have enrolled in clinical trials.²⁵ Furthermore, older patients taking part in trials likely differ from those not on trials not just by a function of their health; they are more likely to be seen at a major medical center or community oncology group where research is a priority and physicians may be more up to date with recent literature. Clinical trial participants may also differ from patients treated outside of trials by socioeconomic factors such as education or income. As such, the excellent efficacy of chemotherapy in elderly colon cancer patients in the aforementioned pooled analyses is an inadequate measure of the effectiveness of treatment in the majority of older patients newly diagnosed with colon cancer.

Colorectal cancer researchers have made use of the Surveillance Epidemiology and End Results (SEER) database linked to Medicare claims to reduce the likelihood of selection bias in their comparisons of the outcomes of those receiving treatment to those not treated. Their hope is that SEER data will improve their estimates of the true effectiveness of adjuvant colon cancer therapy. SEER gathers data on incident cancers through selected US cancer registries, and currently represents approximately 25% of the

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population.³² Approximately 93% of Medicare claims for persons over 65 have been matched to their SEER registry information,^{32,33} and can be used to investigate surgery, radiation, and chemotherapeutics delivered to Medicare recipients.

In 2002, two separate investigators used the SEER-Medicare linkage to ask if fluorouracil-based adjuvant chemotherapy improves mortality in older patients treated outside the venue of a clinical trial.^{34,35} Both studies' investigators attempted to account for inherent differences between people who were treated with adjuvant therapy and those who were not by adjusting for factors known to be associated with colon cancer outcomes using a propensity score. Both with and without adjustment by propensity score, older patients in the SEER-Medicare database who were treated with adjuvant fluorouracil had a lower chance of dying than did those who did not receive adjuvant therapy. The 25-35% reduction in the risk of death seen in these investigations is similar in magnitude to the benefit of fluorouracil seen in clinical trials.²⁶ Preliminary data presented to date in abstract form only suggests that the effectiveness of combination chemotherapy in older patients may also be as robust in the community as in clinical trials.³⁶

In addition, despite their advanced age, older patients with node positive colon cancer who forego chemotherapy are more likely to die of colorectal cancer than from other causes. Deborah Schrag and her colleagues from the Memorial Sloan Kettering Cancer Center noted that amongst Medicare recipients ages 75 to 84 with stage III colon cancer, most of whom did not receive chemotherapy, colorectal cancer was by far the most common cause of death, suggesting that a number of these deaths may have been preventable with the use of adjuvant therapy.²²

Chemotherapy use declines with age

Despite its efficacy, chemotherapy use declines with patient age.^{22, 37-42} In 1995, five years after a National Institutes of Health consensus conference declared adjuvant chemotherapy the standard of care for colorectal cancer with lymph node involvement,⁴³ fewer than one half of patients 75-79 and fewer than a quarter of patients over 80 received adjuvant therapy.⁴¹ In comparison, 78% of patients under 55 were treated with adjuvant chemotherapy for their cancer.⁴¹ By 2000, this trend was largely unchanged, suggesting that diffusion of information about adjuvant therapy effectiveness did not underlie the lack of use in the elderly.⁴²

Ideal care in a non-ideal system: how costly care impairs equitable delivery

There can be little doubt that more elderly patients with stage III colon cancer, given our current health care goal of providing ideal care to each individual, should receive chemotherapy. Indeed, given the apparent tolerability and benefit of adjuvant chemotherapy in the elderly, it is hard to argue that expanding chemotherapy use might not improve colorectal cancer outcomes for many elderly cancer patients who currently go untreated. However, when considering how to maximize the quality of care in the elderly, we must also address how promulgating increasingly costly care for a growing segment of our population will affect the delivery of cancer care.

Reducing conflict over, and inequality in, delivery of cancer care

A rigorous application of standards of "justice" in cancer care delivery requires the elucidation of four points: that we do, in fact, have a positive right to health care; that the positive right includes such advanced and costly care as cancer therapy; that "justice" requires treating relevantly similar interests the same; and that "other things are equal," between patients – that is, that the reasons different patients may be treated differently are *not* reasons that affect whether their interest in treatment is relevantly similar.

Without asserting that justice, in these terms, requires equality of care, we can, nonetheless, make specific claims about particular inequalities in treatment, and the growing conflict these inequalities engender between professional commitments to patient care – the focus on "doing everything" for a given patient – and caring for whole communities or populations of patients.

We have already seen that the cost of cancer care has been rising, fueled by new discoveries in molecularly targeted agents and our desire to provide ideal care. Using the case of adjuvant therapy of the elderly with stage III colon cancer we shall now investigate a practical example of the extent to which our desire to optimize each individual person's care may be financially untenable for CMS, and why it puts justice in cancer care at greater risk.

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Cost of adjuvant chemotherapy for colon cancer

As with all cancer care, largely because of the emergence of new drugs, the cost of colorectal cancer chemotherapy has risen rapidly in the past decade. Until the mid-1990s fluorouracil, still the backbone of colorectal cancer therapy, was the only available drug. In the fluorouracil era, chemotherapy treated patients with metastatic colorectal cancer could expect to live approximately 12 months compared with 6-9 months without treatment.⁴⁴ Similarly, patients treated with adjuvant fluorouracil could expect a 20-30% reduction in their risk of colorectal cancer recurrence after surgery.²⁶

In 1996, the modern era of chemotherapy was ushered in with the FDA approval of irinotecan for use in metastatic disease. Approval of capecitabine (1998), oxaliplatin (2002), bevacizumab (2004), cetuximab (2004), and most recently panitumumab (2007) rapidly followed. With the arrival of this modern chemotherapy era, the outlook for many colorectal cancer patients has markedly improved. The median survival for patients with metastatic disease is now upwards of 2 years,² and by adding oxaliplatin to fluorouracil as adjuvant therapy the risk of cancer recurrence falls by another 25%.²⁷

The advent of these new therapies has clearly decreased morbidity and mortality from colorectal cancer; however, their cost is astounding. In the example scenario we have been discussing of 6 months of adjuvant therapy for stage II or III colon cancer, drug costs alone for the most commonly used regimen (FOLFOX) are around \$36,000 (Table 2).⁴⁵ This figure does not include the cost of nursing services, routine supportive medicines such as anti-emetics, red or white cell growth factors, or the time costs for patients and their family.

Table 2, Estimated Cost of Various Chemotherapy Regimens

Regimen	DRUG COST		TOTAL COST for ELDERLY*	
	8 weeks	6 months	Treating 55%	Treating 75%
#Bolus FU/LV	\$304	\$912	\$21 million	\$29 million
Infusional FU/LV	\$263	\$ 789	\$ 18 million	\$25 million
FOLFOX	\$11,889	\$35,667	\$823 million	\$1.12 billion
FOLFOX/bev	\$21,033	\$ 63,009	\$1.46 billion	\$1.98 billion
FOLFOX/cetux	\$33,183	\$99,549	\$2.23 billion	\$3.14 billion
FOLFOX/bev/cetux	\$42,327	\$126,981	\$2.93 billion	\$4.00 billion

Drug costs based on 95% of average wholesale price in 5/2004 from Schrag.⁴⁵ *
Assuming 150,000 new CRC cases/year, 70% pts >65, 40% with high risk stage II or stage III disease. # Most commonly used regimen before 2004. FOLFOX/bev/cetux and FOLFOX/cetux are not FDA approved combinations. Abbreviations: NA, not used for adjuvant therapy; FU, fluorouracil; LV, leucovorin; FOLFOX, fluorouracil/leucovorin/ oxaliplatin; bev, bevacizumab; cetux, cetuximab.

Furthermore, the cost of adjuvant therapy will likely rise. Ongoing phase III cancer cooperative group clinical trials incorporate the biologic agents bevacizumab and cetuximab into adjuvant therapy with FOLFOX. The results of the first of these trials is expected in the summer of 2009, and if any finds a statistically significant difference in disease-free survival at 3 years, the combination regimens of FOLFOX-bevacizumab or FOLFOX-cetuximab will likely become a routine part of adjuvant colorectal cancer therapy in the United States. If so, drug costs alone for 6 months of adjuvant therapy would fall between \$60,000 and \$120,000 per patient.

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Cost of expanding chemotherapy use in the elderly

Of the 150,000 colorectal cancers diagnosed each year, 70% occur in people over the age of 65. As at least 40% of these patients have lymph node positive or high risk lymph node negative colon cancer, approximately 42,000 people over the age of 65 are eligible for adjuvant therapy each year.⁴ We currently treat approximately 55% of those over 65 with adjuvant therapy.²² Advocates of expanding chemotherapy use in to more older patients suggest increasing the proportion treated and increasing the proportion treated with FOLFOX, the more aggressive and more effective regimen. Currently, of those treated with adjuvant therapy the majority are likely treated with fluorouracil, so the cost of adjuvant therapy is currently between 21 (if all receive fluorouracil) to 800 million dollars (if all receive FOLFOX)—likely closer to 21 than 800 million. If we were to increase chemotherapy use such that 75% of older patients were treated with FOLFOX, the annual cost would increase to just over 1 billion dollars. If we were to incorporate cetuximab into adjuvant therapy the cost would increase to 3.1 billion dollars per year. Thus, expanding therapy as advocated to use more FOLFOX in more older patients might increase the cost of drug fees alone by nearly a billion dollars a year to ensure ideal care for 42,000 people.

Rising costs and failed justice

An ideal medical system would perhaps not flinch at the thought of spending an additional billion dollars per year to decrease the risk of colon cancer recurrence in

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42,000 older patients. Such a system would have no limits to spending, allowing the goals of providing optimally beneficial care and providing care to all to coexist as rational goals for the health care system. Unfortunately, however, no health care system has unlimited funds. As Milton Weinstein of Harvard University explains, the only alternatives in a system with limited funds are compromises, “either with the principle of universal access, or with the principle of unlimited care.”⁴⁶[p268] In America, we have been unwilling to compromise our access to unlimited care, as demonstrated perhaps best by the case of the approval of erlotinib for metastatic pancreas cancer at approximately \$15,000 for an average of 10 days prolongation of life. In the treatment of older cancer patients, funded largely by CMS, our desire for unlimited care has forced us to compromise in our ability to provide care to as many cancer patients as we would like.

Responses to rising cost of cancer care: MMA

It was in this setting of rising cancer cost, with an increasing public contribution to overall health care spending,¹⁶ that the Medicare Prescription Drug, Improvement, and Modernization Act was passed in 2003. As a means of cost containment, the MMA targeted the cost of cancer drugs reimbursed by Medicare Part B by enacting a marked revision of the payment schedule for Part B drugs, the vast majority of which are delivered to cancer patients.

MMA changes in chemotherapy reimbursement

Before 2004, Medicare reimbursed for chemotherapy (and all Part B eligible drugs) at 95% of each drug's annual wholesale price (AWP). The AWP was calculated from prices listed by vendors for chemotherapy; however, as chemotherapy providers (e.g. hospitals and outpatient physician practices) negotiate purchase price with vendors, just as a new car's sticker price is almost never the price agreed upon by the dealer and the new owner, the AWP is not reflective of the actual transaction price. Rather, by negotiating and buying drugs at prices substantially below AWP, chemotherapy providers made substantial profit from the purchase and subsequent delivery of Medicare reimbursed Part B drugs.

This profit margin allowed oncology practices to flourish financially. Not only did the profit afforded by the AWP reimbursement formula cover high salaries for many practicing oncologists, but it also allowed oncology practices to cover the cost of drug delivery by specialty trained oncology registered nurses and the administrative costs of the practice. The AWP-generated profit also allowed community oncology practices to treat at a loss a proportion of uninsured and underinsured patients unable to meet their high copayments without putting the practice at undue financial risk.⁴⁷

In 2004 all of that changed. The MMA called for a transition from paying AWP to a new formula in which drugs are reimbursed at their average sales price (ASP) plus 6%. The ASP is calculated from the actual average transaction cost between vendors and providers in the prior two quarters. The MMA reform allowed for a two year transition: Drugs were reimbursed at 85% of AWP plus 32% in 2004, at 106% of ASP plus an additional 3% in 2005, and by 2006 reimbursement reached the MMA goal of 106% of

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ASP.⁴⁸ The MMA also created a competitive acquisition program (CAP) in 2006. In the CAP, physician groups would be allowed to opt into a program where all drugs were to be supplied by Medicare. Medicare would purchase drugs from vendors by accepting the lowest bids, and then supply them directly to providers' offices. Payments would then go directly to vendors from Medicare, and patients would be billed the copay by the vendor. However, presumably given the low level of reimbursement expected from Medicare, no bids were offered from vendors and this program has been temporarily put on hold.⁴⁹

To offset the MMA mandated decrease in drug payments, chemotherapy providers were asked to bill for chemotherapy delivery services according to the amount of work performed (e.g. intravenous push of chemotherapy or an hour long infusion). No provision was made to cover the indirect costs of patient care.

A major goal of chemotherapy reimbursement reform in the MMA was to contain costs by correcting what was seen as an overpayment for chemotherapy services. At the time of MMA enactment the Medicare Payment Advisory Commission (MedPAC) was directed to provide Congress with reports on how the MMA had influenced cost and services. In the MedPAC January 2006 and 2007 reports, the Commission noted that despite increasing use of oncology services, reimbursement for drugs under Part B drug remained largely unchanged in 2005 and 2006.^{49, 50}

Consequences of MMA reimbursement reform

Though effective in containing costs for CMS, the MMA drew criticism from the media, physicians, and patient groups because of perceived financial risks to oncology

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practices and the Medicare beneficiary with cancer.⁴⁷ Of particular concern was the fate of small, often rural, oncology practices that were perceived as less able to withstand financial pressure imposed by reduced drug reimbursement. The patient and physician groups were also concerned about the fate of underinsured Medicare beneficiaries who might now be expected to come up with 20% copays for astronomically expensive treatments.

Burden of MMA on the outpatient oncology clinic

Critics of the MMA argued that its reimbursement reform places a significant financial burden on oncology providers likely to result in changes in how practices are managed and how care is delivered. In 2003, 80% of chemotherapy infusions took place in outpatient physician offices.⁴⁹⁻⁵¹ Under the new reimbursement rules, however, Medicare drug payments might no longer cover the cost of chemotherapy delivery in the outpatient office setting. In particular, though drugs and nursing care are theoretically reimbursed in full, there is no provision for indirect cost or unpaid bills.

Though it is too early fully to assess how changes in reimbursement truly affect the financial viability of office-based oncology practices, there does already appear to be reason for concern. In their 2006 report to Congress, MedPAC reported the results of interviews with physicians in all regions of the U.S. Physicians and office managers reported that since the institution of MMA reimbursement reform they have spent more time and resources on the acquisition of drugs, in some cases hiring specific purchasing personnel. Financial constraints have forced some practices to cut benefits for staff, substitute part-time for full-time employees, and to replace trained oncology nurses with

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pharmacy technicians to save money. Most frightening, perhaps, was the admission of some physicians that the reform caused them to choose patients based on their ability to pay.⁴⁹

If, as the MedPAC report suggests, under the new Medicare payment structure outpatient oncology practices cannot cover direct and indirect costs of chemotherapy delivery, they will have to find a way to shift the financial burden elsewhere or eventually close. In particular, practices will need to make a decision about how to handle money-losing cases such as chemotherapy regimens where the cost of delivering care is greater than Medicare reimbursement and cases where Medicare beneficiaries are unable to meet their 20% copay. There are two clear options in such cases: treat in a hospital-based setting or do not treat.

By shifting delivery of chemotherapy either to a hospital run outpatient clinic or an inpatient chemotherapy ward, oncology practices transfer the cost of indirect chemotherapy services such as drug purchasing, billing, and other administrative duties to the hospital. In addition, because Medicare reimburses hospitals for up to 70% of copays not met by Medicare beneficiaries, hospital infusion clinics run a much lower financial risk when treating Medicare patients responsible for 20% copays.⁴⁹ Because most physicians are affiliated with hospitals already, shifting care to hospitals would not change the continuity of most physician-patient relationships.

The potential financial consequences of reimbursement reform are perhaps greatest in small oncology practices and rural clinics. Small practices have always been less able to negotiate with vendors for low drug prices, yet they previously earned enough from the AWP reimbursement formula to overcome this disadvantage. In the new model,

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reimbursed at ASP + 6%, small practices without negotiating power will be less able to get drugs for below the ASP. Since the ASP is calculated from actual transaction prices from the previous quarters, the ability of larger practices to negotiate a lower price drives the ASP down, further hurting the small practices. This already appears to be the case: the 2006 MedPAC report found small practices were unable to purchase 15% of the most commonly used drugs at or below ASP. The MedPAC report of 2006 also noted that a number of larger practices have been able to supplement their income by adding diagnostic capabilities to their practice (e.g. positron emission tomography scanners); smaller practices do not have the capital to undertake such costly expansion.⁴⁹

Thus, the MMA reimbursement reforms clearly put pressure on oncology practices. Such pressure may well lead to a shift in the site of cancer care to hospital-based settings, and is most likely to affect the financial stability of smaller practices.

The cost to the disadvantaged Medicare beneficiary

Though the MMA reimbursement reform will strain the financial stability of outpatient oncology practices, the majority of large practices will likely be able to restructure their practice in a way that allows them to continue to function in a fashion quite similar to the pre-MMA era. Similarly, patients with private insurance or Medicare with supplemental insurance living within reasonable proximity of a large oncology practice will likely notice few differences in their cancer care. Unfortunately, however, poor Medicare recipients without supplemental insurance and small practices, often located in rural areas, are likely to feel the sting of the MMA reform. Thus, it is the poor

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and the rural-dwelling cancer patients who are likely to be affected adversely by the MMA.

Rural communities tend to be served largely by small practices or rural satellite clinics operated by large practices in neighboring towns. As the MMA squeezes both small and large practices they will be forced to restructure their spending. For large practices operating satellite clinics at a loss for the community, an early cost-cutting maneuver may be to do away with the money losing satellite. Small practices will feel the financial pressures most and may be forced to turn away patients unable to pay or be forced to operate at a loss—a prospect that cannot go on forever. Whether small practices and satellites close or simply turn-away poor patients, either option would leave the rural communities they serve without adequate cancer care.

In addition, it is the poorest of Medicare patients who are most likely to suffer if outpatient practices transfer chemotherapy delivery to hospital-based settings when reimbursement fails to meet the practice's cost. Hospital-based services are both more expensive and less efficient than outpatient oncology clinics. Thus, the out-of-pocket expenses for Medicare beneficiaries will increase if they are shunted to hospital-based clinics. In addition, shifting the patient's infusion to the hospital run clinic will mean many clinical and administrative services will be duplicated, such as blood draws and vital signs, thereby increasing the practical time burden on patients.⁴⁹ Because of their inability to meet copays, it is the poorest Medicare patients who are mostly likely to be referred to hospital-based infusion clinics. Thus, the patients who already have worse cancer outcomes—the poor and the rural dwelling—are most likely to be harmed by the new financial pressures of the MMA reimbursement reforms.

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Will these fears be realized?

Though the new payment structure clearly favors large practices and the referral of patients without supplemental insurance to hospital clinics, it is not yet clear if these forecasted changes in practice pattern will truly happen.

In 2005 the National Patient Advocate Foundation contracted the Duke University Center for Clinical and Genetic Economics to investigate whether there had been any change in the site of chemotherapy administration, the time until chemotherapy initiation, or the patient perceived ease of referral from 2003 (pre-MMA) to 2004. Using Medicare claims data, the Duke study found no differences in the site of care or the length of time until treatment was initiated.⁵¹ In addition, an internet survey of self-selected cancer patients found no difference in the perceived ease of referrals for or receipt of chemotherapy between 2003 and 2004. A subgroup analysis showed a hint that rural patients and patients without supplemental insurance were more likely to be treated at a hospital-based clinic, however the numbers of such patients were too small to allow for adjustment for potential confounding factors such as comorbidity.

As noted by its authors, the Duke study was probably conducted too early truly to assess MMA-related change in chemotherapy practice. Even though drug reimbursements fell in 2004 they were still substantially above the reform's target. In addition, payments to oncology practices from the Medicare Quality of Life Demonstration Project served to cushion the blow of falling reimbursement. The Demonstration Project, initiated concurrently with the MMA reforms, paid participating oncology practices \$130 per patient per visit to ask Medicare patients three questions about fatigue, nausea, and pain. Thus, combined with reimbursement at AWP + 32%, participating practices still brought

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in a substantial sum of money for treating Medicare patients in 2004. Furthermore, though well intentioned, the Duke internet survey respondents were self-selected oncology patients motivated and savvy enough to find and respond to a survey about their care. Their responses are not likely representative of the majority of Medicare beneficiaries.

The 2006 and 2007 MedPAC reports, however, are more alarming. Both years the Commission reported that, as predicted, small oncology practices were more likely to be affected by the reimbursement reform.^{49, 50} The Commission also reported that compared to Medicare beneficiaries with supplemental insurance, those without supplemental insurance were more likely to receive chemotherapy in a hospital-based inpatient or outpatient setting. Though the commission found no evidence that the quality of cancer care was diminished by the MMA mandated reimbursement reforms, they readily acknowledged that measures of quality are complex, and they were not equipped adequately to address that question.

Though MedPAC reports to Congress from March and June of 2008 do not focus on the consequences of the MMA on cancer therapy, they both stress a serious concern about Medicare's long-term sustainability in the setting of rising costs and an increasing number of baby boomers almost ready to enroll in Medicare. The March 2008 report notes that viability will require both a reduction of expenditures and new financing,⁵² neither of which has been enacted with the exception of decreasing reimbursement. This report also notes that with the current trajectory, the burden of cost sharing borne by patients will increase; though beneficiaries are likely to continue contributing a stable 12-13% of the program's revenue through premiums and copays, this will make up an

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increasingly large proportion of beneficiaries' income as costs rise and social security does not. The nearly 50% of Medicare beneficiaries with yearly incomes less than \$20,000 dollars are most likely to feel the sting of this cost sharing.

Cost-containment: moving toward a more equitable policy paradigm

We have seen that current policy efforts have focused on controlling cost to the payer by shifting cost to physicians, hospitals, and cancer patients. None, however, have directly addressed the underlying cause of increasing cost: with our gold standard for quality being ideal care for each individual, we are unwilling to deny any patient a drug that provides even marginal anti-cancer benefit. If this continues to be our goal, and we fail to act now in a proactive fashion, CMS will be forced to make difficult decisions about reimbursement. Without the political will to deny the most costly treatments, CMS's only means of cutting cost will again be to shift it towards another party. This path seems to lead us to a system of cancer care in which costly ideal care, improving all the time with new discoveries and drugs, will be available to those Medicare patients able to afford supplemental insurance or high copays, while many—particularly the disadvantaged—receive suboptimal or no care at all. The time for action is now, as these negative effects of rising cost have already begun to jeopardize American health care. Indeed, the 2007 report of the Medicare Board of Trustees concludes that financial issues resulting from the rising cost of care demonstrate the “need for timely and effective action to address Medicare's financial challenges”.⁵³

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I believe the best way to address this rising cost and the resultant rising imbalance in cancer treatment is collectively to re-evaluate the framework from which we have made decisions about American health care. Our current goal—to provide ideal cancer care to each individual—can only be just if resources are unlimited. In such a case, each older colorectal cancer patient could receive 6 months of FOLFOX at \$36,000, or 6 months of FOLFOX-bevacizumab at \$63,000 without drawing resources from another cancer patient. However, it is patently clear that resources in our health care system are not unlimited. Thus, the only way for us to provide care that is just is for us to re-define quality care as that care which is optimal for *all*,⁵ accepting that many may receive care that is no longer "ideal." In such a scenario we may be willing to treat all patients with FOLFOX, but decide that we are unwilling to pay \$30,000 more for the marginal benefit afforded by the addition of bevacizumab.

We will only be successful in redefining our notion of quality therapy if we can garner the collective will to do so.⁴⁶ Without the backing of physicians, those who ultimately chose which therapy to administer, many might continue to strive for ideal care for each of their own patients, leaving other, unseen patients with less care. Similarly, patients as consumers must be willing to accept that justice in health care ought to be one of our guiding principles, and that they may have to sacrifice their unlimited access to care so that all cancer patients can receive good treatment. And though the notion of sacrifice has become distinctly un-American, now is the time for that to change.

Building patient support

Such collective acceptance of a need to re-frame the goals of our health care system will be difficult, as for decades the notion of entitlement to the best available care has become an American way of life. Even patients without effective treatment options clearly want more care. In a survey of patients enrolling in phase I oncology trials (in which the trial goal is to assess the safety of the new agent without any expectation on the part of the investigators of clinical efficacy), only 7% had seriously considered getting no additional cancer treatment despite having received many prior lines of therapy for incurable disease.⁵⁴ Furthermore, 90% of these phase I trial enrollees reported they would be willing to accept a 10% risk of death for access to the experimental drug. These figures are despite the fact that the likelihood a patient will benefit personally from enrollment is quite small: approximately 4% experience reduction in cancer size when participating in a phase I trial of a new chemotherapy.⁵⁵ Even at the end of life, many American cancer patients seem to prefer receiving more anticancer therapy, even with a marginal benefit and substantial risk.

But, patients have already begun to feel the untoward effects of rising costs. Americans currently pay approximately 13% of their medical costs out of pocket,⁵⁶ a proportion that represents a larger and large absolute value as costs rise. In addition, premiums for private insurance for a family increased 73% from 2000 to 2005, compared with an inflation rate of 14% during the same time period.⁵⁶ The strain of these costs appears to be affecting Americans' ability to access good care. In 2006 survey, 43% of Americans living with a cancer patient reported having to choose suboptimal care (e.g.

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skipping treatment, cutting pills, or not filling a prescription) because of cost.⁵⁷ This difficulty paying for needed care extended to all Americans, not just those with cancer: 23% of Americans reported having a difficult time paying their medical bills, 61% of whom were insured. In a Kaiser Foundation Daily Health Report from July 8th, 2008, noted bioethicist Arthur Caplan of the University of Pennsylvania is quoted as saying that the high cost of cancer drugs is “one of the toughest issues in oncology” as high drug prices can mean trading “family assets for a few more months of life”.⁵⁸

The rising cost of prescription drugs is a main contributor to the cost burden of medical care on families. Recently, the high prescription drug cost has led 86% of Medicare part D providers and 10% of private insurers to decrease their benefits for expensive prescription drugs through the creation of a “Tier 4” payment scheme.⁵⁹ Drugs selected for inclusion in Tier 4 are covered, but the patient must pay typically between 20-33% of the cost—a figure that may be in the hundreds of dollars per month. A New York Times article about this change notes that insurers claim this new system allows them to keep premiums down for healthy subscribers by shifting the cost of these extremely high price drugs to the sick enrollees.⁵⁹ The article highlights the effect of this Tier 4 scheme on patients with severe or life-threatening chronic illnesses such as multiple sclerosis, chronic myeloid leukemia, and metastatic breast cancer. The individuals interviewed for the article stress how this new payment system has forced them to chose between paying for their medicines and paying for other crucial life events, such as their children’s education.

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As a result of these difficulties, 86% of Americans believe that the US health care system needs to be fundamentally changed or to be completely rebuilt.⁵⁷ And despite arguments against a national health plan that might require rationing or limits in choice as do the Canadian and British systems, three times the number of Americans are dissatisfied with the health care system as are Canadian and British citizens.⁵⁷ Seventy percent of Americans also believe that the US government should be paying more for health care,⁵⁷ signaling Americans may well be open to more government involvement in how our health care system operates.

Thus, though Americans continue to want ideal care—even want care from which they have an exceedingly small chance of benefiting—all but the wealthiest of Americans have been affected by the rising price of American health care; and, importantly, most Americans recognize that a fundamental change in the structure of our health care system is needed. As such, with the right support, the American people could likely be encouraged to reconsider the paradigm from which our health care decisions are made.

Securing physician support

Just as many cancer patients report wanting to receive treatments that offer even the smallest hope, their physicians want to be able to offer them such treatments without regard to the implications of the treatment decision outside the confines of what is best for that patient. Though American physicians are not unique in their desire to provide the best possible care for their patients, those practicing in many other countries have been

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able to work successfully from a framework where providing care is more important than providing ideal care for the individual.

Perhaps as a result of inherent differences in the underlying goals of our health care systems, the oncology treatment culture in the U.K. is much different than our own, exemplified in the conduct and interpretation of a recently completed phase III trial in metastatic colorectal cancer. The FOCUS trial was conducted in the U.K. in the late 1990s through the early 2000s.⁶⁰ In this trial the sequential use of single agent chemotherapy drugs (fluorouracil or irinotecan) was compared to the upfront use of combinations of irinotecan, oxaliplatin, and fluorouracil. Median survival for the patients treated with single agent therapy was approximately 14 months, while those treated with initial combination chemotherapy survived an average of 16 months. The British authors concluded that survival was not improved by the more aggressive therapy, and they have continued to conduct studies that include single agent arms. On the other hand, American oncologists largely used this trial to argue in favor of combination therapy as the standard of care,² and American cooperative oncology groups no longer conduct trials of single arm therapies. Certainly, both groups are correct to some degree: from the standpoint of advancing research, combination therapies are likely the best platform from which to build. However, single agent therapy should be an accepted treatment option for all patients with metastatic colorectal cancer, and may be a less costly way to get cancer care to all Americans.

Clearly, less costly and slightly less effective treatment options are available for routine clinical use; yet, a physician's primary obligation is to their patient.^{46, 61}

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Confronted with the choices offered by the FOCUS trial, of whether to offer a 69 year old otherwise healthy woman with stage IV colon cancer the less effective and cheaper fluorouracil or the more effective and more costly FOLFOX, a physician should not have to consider how giving FOLFOX to this patient will diminish Medicare's coffers. Rather, the physician should discuss the options with the patient and make the correct decision for that patient. Unfortunately, cost has become an issue in the routine practice of oncology. In a survey of practicing oncologists, 42% report routinely discussing chemotherapy cost with patients.⁶² Yet, placing such decisions in the exam rooms erodes the essence of the doctor patient relationship.⁶¹ Similarly, cost-containment measures that seek to use differential reimbursement as an incentive for physicians to select cheaper care force the physician to choose between society and the individual ill, vulnerable patient who sits before them.⁴⁶ We should not rely on the doctor to be the gatekeeper of change; rather, change should be directed by a national understanding of our need to contain costs and be mandated at the level of national policy.

Physician support of change, however, will be essential if any real change is to take place in how care is delivered in the US. Just as patients have to pay more as a result of the rising cost of American medicine, physicians have also felt the sting of decreased Medicare reimbursement, suggesting they may be open to supporting policy change. In a survey of 8,955 physicians conducted by the American Medical Association regarding the effect of the 5% cut in Medicare reimbursement recommended for 2008, 45% of responding physicians reported they would be forced to either decrease or entirely stop accepting new Medicare patients.⁶³ Furthermore, 72% said they would be forced to defer the purchase of new medical equipment, and 67% would defer the purchase of new

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information technology (a clear concern given the importance of information technology in decreasing errors and generally improving the quality of medical care).

Given that the cost of delivering medical care is not likely to fall in the near future, declining reimbursement in the setting of rising costs will continue to place physicians in a financially difficult position, perhaps opening them to the thought of redefining optimal quality care.

Perceptions of the medical elite

In order to assess the climate within the academic medical community with regard to cost and cost containment measures for cancer therapies, I conducted a systematic review of the medical literature. I search PUBMED using the following terms: cost; cost-effectiveness; cancer; chemotherapy. The search was limited to English language articles published between January 1, 1990 and June 30, 2008. In addition, the search was limited to clinical trials and editorials. I chose to include editorials in this search because a main goal was to assess the climate for change amongst the academic oncology community. As opinions and conjecture are most likely to be included in discussion sections and editorials, these were the primary sites of the search. This search yielded 291 potentially eligible articles. Abstract review narrowed this field to 17 articles possibly meeting the entry criteria of: discussing cancer chemotherapy and cost AND discussing solutions, policy, or opinion regarding cost management. Eleven articles⁶⁴⁻⁷⁴ met the eligibility criteria and are included in the review.

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A major theme of the reviewed papers was the notion that health care resources are finite. As such, deciding to accept a new drug or treatment for use in clinical practice, even if deemed relatively cost-effective, requires shifting resources from another service—perhaps from other health care services, or possibly from other societal services such as infrastructure or education. In their commentary on the cost of trastuzumab for breast cancer therapy, Drs. Hillner and Smith of the Massey Cancer Center note that the US drug approval and reimbursement system has generated a perfect storm of cost increases: patients want access to new drugs and technology and meanwhile are relatively protected from the cost of these new therapies by only having to pay co-payments; the FDA does not negotiate drug prices with manufacturers; and Medicare does not consider cost in reimbursement decisions.⁶⁴ And, because of this increasing cost, without action to increase the pool of resources, such as dramatically increasing taxes, clinical use of even extremely effective drugs such as trastuzumab means diverting funds from another service. Such divergence of funds is also noted by Drs. Ramsey and Kessler, principally the decline in physician reimbursement by Medicare.⁷² Drs. Elit, Gafni, and Levine of McMaster University in Ontario further note that within a fixed budget, it is best to look to cut inefficiencies within the same system—in their case the treatment of cervical cancer—rather than to divert resources from distant sources.⁷⁴

The American medical elite were in agreement that there should be a greater, more transparent national discussion of the cost of cancer treatment. Hillner and Smith believe that cost-effectiveness must be taken into greater account in decision-making about the availability of cancer therapies,⁶⁴ and Ramsey and Kessler call for an open dialogue about the cost of care.⁷² Ramsey and Kessler go on to say that the medical elite,

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namely the National Cancer Institute funded Cancer Cooperative groups that serve as the thought leaders of cancer therapy, should both include cost-effectiveness analyses as part of clinical trials and consider cost when making decisions about what drugs to include in future clinical trials as these trials ultimately dictate what drugs will be used in routine clinical practice.⁷² In their commentary on the editorial by Ramsey and Kessler, Roberts, Lynch and Chabner concur that the cost of care is high, but strongly caution against any incorporation of cost into direct patient treatment decision-making, noting that such considerations are antithetical to physicians' ethics.⁷³ They do agree, it seems, that a "macro-level" discussion about cost would be appropriate, but that in the US there is no real venue in which to have this discussion as there is no central health system to guide decisions and no guiding principles are available to help incorporate ethics and individual preferences into health economic decisions. Perhaps because of these short-falls, they title their commentary, "Choosing chemotherapy for lung cancer based on cost: not yet".⁷³

Bartley Madden, an "independent researcher" from Naperville, Illinois, proposes more specific means of containing cost. In his commentary he notes that one of the main drivers of the high cost of pharmaceuticals is the FDA approval process that requires complex and costly clinical trials to demonstrate efficacy and safety; this process drives up the cost of drug approval to the drug developer, and is eventually borne by the consumer.⁷¹ He proposes a trial of a new dual tracking system for FDA approval, in which drugs may follow the traditional pipeline through FDA approval, or may chose to go through a process that allows for greater freedom of choice. This freedom of choice track would permit patients and physicians to purchase from a distributor drugs that have

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passed phase I trials without any significant concern for safety. Though minimal or no efficacy data would be available on these drugs, Madden argues patients and physicians are capable of understanding that notion: those unwilling to take the risk would not make use of this track, while those with fatal diseases for which no treatments are available—he uses the example of Amyotrophic Lateral Sclerosis (Lou Gehrig’s Disease)—would have access to potentially beneficial medications. Madden argues that this process would speed drug discovery as a larger number of patients with a variety of ailments would be exposed to the drug and data on their outcomes would be a requirement of participation. He also argues that this dual tracking method would serve as a feedback mechanism for the current FDA process—pointing out where inefficiencies and waste are common.

In contrast to the American comments that focused largely on the unregulated cost of cancer care, comments from the other, largely British, authors focused on criticisms of the cost-containment measures already in place. These criticisms are largely representative of frustration in the ability to gain access to drugs, with comments focused on the UK’s National Institute for Health and Clinical Excellence (NICE). In response to an article by Jönsson and Wilking about the uptake of new cancer drug therapy that noted drug uptake in the UK was among the slowest, that criticized NICE as the cause of this slow uptake, and further noted cancer mortality in the UK is among the highest in Europe,⁷⁵ the editorial staff of the *Lancet* noted that the UK needs to decide on a national plan to achieve better survival and more quality adjusted life years. They note that if cost is the only issue being considered, then the system is failing.⁶⁷

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NICE is further criticized in two commentaries about the approval process of bortezomib (Velcade), a proteasome inhibitor approved in the US for use in relapsed or refractory multiple myeloma. Despite bortezomib's superior ability to induce a clinical response and prolong time to tumor progression and overall survival compared with the standard of care in this uniformly fatal disease, it was not recommended by NICE for use in the UK based on the cost of the drug and the modest benefit it offers over other conventional therapies. As a result of public outcry, NICE's decision was altered in June of 2007, allowing use of bortezomib in the second-line treatment of multiple myeloma by way of a cost-sharing plan with the UK distributor, Janssen-Cilag. According to this agreement, the drug was allowed for 4 months. If the patient did not respond, the company reimbursed the National Health Service (NHS) for drug costs. These decisions, both the original rejection and subsequent limited approval, raised a number of important concerns about NICE's approval process. Eric Low, the Chief Executive of Myeloma UK, noted that the current mechanism for drug approval through NICE often does not result in a "fair or sensible treatment availability", as was the case in the bortezomib decision.⁶⁹ In particular, he criticizes the arbitrariness of the QALY and the pre-set cost-limits that do not allow for fair consideration of a costly drug for a disease such as myeloma with a short life expectancy. The concept that the current cost-effectiveness as inappropriate for drugs used in terminal illness was echoed in the discussion of a cost-effectiveness analysis of cetuximab as third line treatment for colorectal cancer in which the authors note with a short survival the absolute benefit of a drug will always be small, driving up the cost-effectiveness ratios; they argue in the case of terminal illness with short survival, higher cost should be allowed.⁷⁰ Low concludes by suggesting greater

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transparency in the review process, and an open discussion about means for reform. Also in response to the bortezomib decisions, the editorial staff of *Lancet Oncology* suggested that rather than using rebate schemes to allow for limited approval of drugs, NICE should look into lowering the cost of drugs by better regulating the pharmaceutical industry. They acknowledge, however, that the US is likely the only country with a large enough market share to negotiate lower drug prices.⁶⁶

The high cost of cancer care has clearly sparked a degree of unrest amongst the academic elite in both the US and the UK. In the US, academic oncologists have only begun the discussion—calling for a national consideration of cost, rather than a specific change. In the UK, the discussion focuses on reforming a cost-containment system to be more responsive to the needs of patients than the need to manage cost. While clearly neither American nor European academic oncologists have presented a comprehensive plan for cost-containment that both lowers cost while maintaining a goal of providing excellent cancer care, many are clearly ready for change. Their support as thought-leaders of the future of cancer care will be paramount to any successful plan to change our outlook on how to deliver care.

Recommendations for reform

No single solution will halt the staggering growth in the cost of medical care in the US. A combination of reforms that tackle inefficiency and waste in addition to the cost of new technology will certainly be needed if we hope to curtail the current projected

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growth that predicts Medicare spending will be 9% of the gross domestic product by 2050.⁵² However, as I hope I conveyed, our national desire to provide ideal care to each and every patient has hampered reform efforts to date, resulting in measures that require patients and physicians to shoulder a greater burden of this cost without addressing its cause.

I believe a critical component to successful cost containment is the establishment of an independent body to review the comparative clinical effectiveness and cost-effectiveness of new drugs and technologies, and to make recommendations about drug approval to the FDA and reimbursement to CMS based on their findings. Such a body would provide invaluable evidence to support approval and reimbursement decisions by the FDA and CMS, and, if done well, could also be a launching point for opening a true national dialogue on our national goals for health—ideal individual care or equitably delivered excellent care for all.

In addition to opening a discussion about cost through this committee, the FDA and CMS must begin to place greater weight on the cost-effectiveness of their approvals and reimbursement decisions, as I fear the best of intentions of the intellectual elite will be insufficient to bring about real change.

Establishment of an independent Effectiveness Committee

I believe an important next step in major reform for our health care system is the establishment of an independent committee commissioned to assess the clinical and cost

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effectiveness of therapies. This Effectiveness Committee would be charged with evaluating new drugs and technologies prior to FDA approval, and providing evidence of comparative effectiveness for already established therapies (see Table 3).

Effectiveness Committee models

In proposing a structure for the Effectiveness Committee, I believe we should take into account the model of the UK's NICE, and incorporate changes to overcome some of the aforementioned criticisms. MedPAC has also suggested the establishment of a similar committee, and I believe most of their recommendations should be adopted.

NICE serves as an excellent model upon which to base our committee. NICE's primary functions are to provide guidance on the promotion of health and the prevention of illness, to evaluate and provide guidance on the use of new treatments by the National Health Service, and to provide guidance on the appropriate treatment and care of people with disease.⁷⁶ Through its Centre for Health Technology Evaluation, NICE conducts appraisals of new drugs and devices with regard to both their clinical effectiveness and their cost-effectiveness. Recommendations are then provided to the NHS about coverage. The NHS is legally required to fund any medication or technology that is recommended by a NICE appraisal.

Establishment of a committee to evaluate comparative clinical effectiveness was also recommended by the Medicare Payment Advisory Committee in 2007 and again in the June 2008 report.⁷⁷ MedPAC recommended the establishment of an independent

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committee funded by federal and private monies to review the comparative clinical effectiveness of new and already accepted treatments. This committee would conduct appraisals transparently, and provide their results to interested parties (payers, providers, and patients). Importantly, MedPAC recommended that the committee have no role in making or recommending coverage or payment decisions based on the results of their studies. In addition, MedPAC specified that the committee could conduct cost-effectiveness research if so desired, but that this should not be the primary aim of the committee.

Proposed Effectiveness Committee structure

First, the Committee should be composed of largely of academic researchers with expertise in cost-effectiveness and comparative effectiveness research; it should also, however, include representatives of all aspects of health care such as representatives of payers (CMS and private insurers), practicing physicians, and patient advocates. These health system representatives should be included as a second task of the committee will be to educate, research and report upon the American public's will for accepting cost as part of drug approval process. As is the practice with NICE, commissions about given technology or drugs would be distributed to contracting teams from academic centers able to conduct rapid assessments. The results of the assessments would be provided to the FDA, CMS, and published in peer-reviewed journals as well as a Committee website.

Secondly, the committee should be charge with two main objectives:

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- Generating comparative clinical and cost effectiveness research on new drugs and devices undergoing consideration of FDA approval, and existing drugs with high cost and concerns of marginal benefit.
- Garnering political will for cost-based decision-making in US health care with the American public and conducting research on public will.

The June, 2008 MedPAC report recommended that the effectiveness committee focus on conducting comparative clinical effectiveness research only, with cost-effectiveness research playing a minimal role only if desired by the committee. I strongly disagree with this soft approach to the conduct of cost-effectiveness research. I believe that should be a primary charter of the committee; providing clinicians with evidence of comparative effectiveness alone may improve the efficiency of resource utilization, but it will not provide adequate information to truly curtail the rising cost of our system. Thus, real cost-based decisions on the availability of drugs will be necessary and the FDA and CMS will need reliable cost-effectiveness data upon which to base decisions.

I do, however, agree with the MedPAC recommendation that the Committee should not have power over funding decisions based upon their findings. Criticisms of NICE can teach us that too much power in such a committee is detrimental to its public acceptance.^{67, 69, 75} The Committee's role in drug approval and funding decisions should be to provide independent, high quality evidence upon which other players can make sound policy decisions.

Table 3, Proposed reforms for curtaining growth in drug and technology costs	
Structure of Reform	Key Points
Committee on Clinical and Cost-Effectiveness	
Independent organization	Public and private funding reduces obligation to serve one party.
Transparency in conduct	Reduce criticisms of decisions
Comprised of research experts with advocates from payers, physicians, patients	- Upholds primary aim of conducting research - Includes voices from interested parties
Not responsible for approval or reimbursement decisions	- Keeps decision-making separate from research - Minimizes questions of bias
Conduct town meetings to inform public	- Initially open dialogue with frequent meetings throughout US - Subsequent meetings twice a year to continue dialogue
Centers for Medicare and Medicaid Services	
Mandated to include cost in consideration of reimbursement	- Use committee's assessments - No preset cut-offs of cost-effectiveness
Mandated to negotiate drug prices	- Huge market share should drive down cost
Food and Drug Administration	
Mandated to include cost in consideration of reimbursement	- Use committee's assessments - No preset cut-offs of cost-effectiveness
Allow for conditional approval with cost-sharing	- Drugs with marginal effectiveness can be approved. - Tight post-marketing surveillance on safety/efficacy - Cost-sharing with manufacturer if ineffective

I also agree with the MedPAC recommendation for a committee funded through both public and private funds. A lesson that might be learned from the aforementioned criticisms of NICE surround its power as both an evaluation committee and an approval committee given the legal mandate of the NHS to fund recommended treatments. Given Americans' reluctance over the years to accept government guided health care, I believe an entity with greater independence from the federal government is more likely to garner public support. By funding it with both public and private money, undue influence from any funder (e.g. pharmaceutical or government) would be minimized.

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Opening a national dialogue

The Committee should also be charged with opening a national dialogue about the cost of care and reform efforts. I propose a town hall meeting approach in which Committee members, aided by a public relations and policy strategist, would bring together Americans to lay out why the high cost of medical care is a problem for them, and why they should support efforts to cut cost. Importantly, these meetings would need to stress the finite resources within health care, and that without change the cost of care has been shifting to the consumer. During the first year of this Committee, meetings should be held throughout the nation. Twice yearly meetings with rotating geographical sites should be held in following years to continue the dialogue and address concerns as they mount. Such meetings would also be a venue for the Committee to conduct research on the American public's political will regarding the use of cost in drug approval and reimbursement decisions, and what cut offs for cost-effectiveness would be acceptable to Americans.

Related reforms within the FDA and CMS

Though the idea that a committee that provides information about clinical and cost-effectiveness will be enough to change practice is a nice ideal, the truth is that our system has grown so accustomed to accepting marginal benefits as improvements worthy of incorporation into practice that change is unlikely to occur without mandating the use of these data by agencies in charge of drug dispersion. Both CMS and the FDA must be made to incorporate cost into their decision-making about new technology, and must be forced to take a harder line against the

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pharmaceutical industry—forcing it to foot the bill for ineffective drugs and making use of our vast market share to negotiate lower prices.

Food and Drug Administration

Currently, cost-effectiveness plays a minimal role in approval decisions made by the FDA: the case of the approval of erlotinib for use in metastatic pancreas cancer with a cost-effectiveness ratio of \$430,000 per quality adjusted life year is a clear example of this. The FDA does even less to limit the dispersion of new technologies, requiring only demonstration of safety, not efficacy, to approve new devices. The FDA, however, is the agency best positioned to incorporate cost into decision-making. I recommend that the FDA be mandated to review the proposed Effectiveness Committee's assessments of cost-effectiveness and comparative clinical effectiveness before approving a drug. I also believe that this should be the case for new devices as well. NICE has been criticized for slowing down drug dispersion through the UK,⁷⁵ a criticism the FDA also faces frequently. A conditional approval system, however, might circumvent this.

By granting drugs approval through the traditional pathway while cost-effectiveness research is conducted by the committee, yet attaching a condition for post-marketing surveillance and cost-sharing, the FDA might be able to decrease the burden imposed by marginally effective drugs on the US health care system. Drugs that prove ineffective in comparative effectiveness research or post-marketing surveillance would be denied. Drugs that demonstrate marginal benefit or a very high cost-effectiveness ratio would continue their conditional approval. Such conditional approval would allow drug companies to market their drug, and ease the clinical

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trials process for development of the drug for other indications. Conditional approval, however, would allow Medicare to demand a cost-sharing proposal at the time of reimbursement decisions. Conditionally approved drugs could receive a form of fast-track re-review in the case of emerging evidence of effectiveness.

Centers for Medicare and Medicaid Services

CMS has always been the leader in reimbursement decisions in the complicated US health care market. As such, I believe changes within CMS to include cost as a consideration in reimbursement decisions would begin a national reform. This should occur in two ways. First, Medicare should consider cost in reimbursement decisions based on the recommendations of the Effectiveness Committee. While NICE has pre-existing cut-offs for what to recommend as cost-effective, I believe Medicare should begin simply by reviewing cost-effectiveness research with each decision. Based on feedback from the Committee regarding what is acceptable to the public, cut-offs could be imposed in subsequent years. Secondly, CMS should use its power as a huge portion of the market to negotiate for lower drug costs. This would take two forms: for drugs receiving conditional approval by the FDA, CMS should demand drug companies foot part of the bill for patients in whom the drug proves ineffective; and, CMS should negotiate lower prices for all agents at the time of their reimbursement decisions.

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Cetuximab for colorectal cancer, a prime example of needed reform

The story of the ImClone drug cetuximab (Erbix) is, I believe, an excellent example of how the proposed reforms could be made to decrease cost while still allowing new drugs to enter the marketplace.

Cetuximab, a monoclonal antibody directed at the epidermal growth factor receptor, was approved in February of 2004 for the use in EGFR expressing metastatic colorectal cancer refractory to irinotecan therapy. Approval was based on the results of a randomized phase II study comparing cetuximab alone to cetuximab and irinotecan.⁷⁸ This study showed tumor regression in 11% of patients treated with cetuximab and 23% of patients treated with cetuximab and irinotecan. Time until disease progression was also 2.6 months longer (4.1 months versus 1.5 months) in the cetuximab/irinotecan arm. No survival difference was noted, though cross-over from the cetuximab arm to the cetuximab/irinotecan arm was permitted at the time of disease progression.

ImClone chose to market cetuximab at approximately \$21,000 for 8 weeks of treatment, approximately \$12,000 more per 8 weeks than the price chosen by Genetech for their blockbuster bevacizumab, also approved in February of 2004.⁴⁵ An assessment by the NICE Centre for Health Technology was unable to calculate a cost-effectiveness ratio for cetuximab as there was no standard arm against which to compare it, however, their estimates suggested it would be well above £30,000.¹² Yet despite the cost, the very common acne-like rash that typically covers the face, and a substantial risk of anaphylaxis, cetuximab was rapidly incorporated into clinical practice as a second or third-line agent, largely because there are few

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therapeutic options available to patients with metastatic colorectal cancer whose disease has progressed on chemotherapy.

I believe that cetuximab would have been an optimal drug for conditional approval and some sort of cost-sharing program with CMS. Cetuximab was approved based on a 10% response rate and a 1.5 month time to progression—hardly a huge improvement in cancer outcomes despite few therapeutic options. However, it was clear from studies that the subgroup of patients who did respond seemed to have substantial benefit from the drug. Further research into who responds to cetuximab has uncovered that the approximately 30% of patients whose tumors harbor mutations in K-Ras (a molecule downstream of the action of EGFR) essentially never respond to cetuximab, while those with normal K-Ras have a 40% chance of response—a figure four times that of the unselected group.^{79, 80} These findings were just recently reported. Cooperative groups and the FDA are reviewing currently the use of cetuximab in ongoing and planned clinical trials. Yet, it is almost certain that approval of cetuximab will be narrowed to patients with a normal K-Ras only. Such an approval markedly enriches the population of responders, and thus clearly improves upon both the clinical and cost effectiveness of this agent.

In retrospect, FDA approval of cetuximab in 2004 generated a huge amount of capital for ImClone at the expense of CMS and other payers, despite the fact that about a third of patients (the K-Ras mutant tumors) had no chance whatsoever of responding to therapy. Given the small benefit seen by patients in the registration trial, this drug may well have been singled out by the proposed new system for conditional FDA approval. Such conditional approval would have allowed ImClone to market cetuximab, continue to collect post-marketing data, and ease the regulations on cetuximab's inclusion in clinical trials under development. Conditional approval

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would also have required that ImClone continue to foot part of the bill for a drug of minimal effectiveness, a strategy that would have saved CMS a huge amount of money. And, importantly, such conditional approval would not have compromised the research that has identified a group of patients—K-Ras wild-type—who is more likely to derive benefit from this drug.

Summary

The cost of all health care is on the rise, and the cost of cancer care leads the way. Attempts at cost containment have shifted the cost to consumers and health care professionals while failing to address to the true reason behind soaring prices. Our national desire to provide ideal care to each individual is truly noble, yet the finite resources available to finance this care do not allow ideal care to be available to all. Though Americans have been leaders in the fight to decrease suffering from cancer through emerging technology, we have failed in our ability to prevent growing inequity in care. As a nation we must face this reality together, and accept that in order to decrease the suffering caused by cancer for all Americans, we must personally be willing to sacrifice our ability to access every drug we might want.

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