

A Quality-Adjusted Price Index for Colorectal Cancer Drugs*

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1 Introduction

Medical technology, broadly defined as the products and services patients receive when treated, is the engine behind increases in medical spending. Newhouse (1992) concludes that approximately two-thirds of the growth in medical costs in the United States between 1950 and 1987 was due to changing medical technologies.¹ There is also evidence that medical care in the US has improved substantially over the past 30 years for certain health conditions such as cardiovascular disease. For example, the life expectancy of a 45-year old today is 4.4 years longer than it was in 1950 (Cutler (2004)).² Murphy and Topel (2006) estimate that the total rise in life expectancy in the US between 1970 and 2000 increased national wealth by \$3.2 trillion per year, which is approximately equal in value to one-half of GDP.

An important policy issue, therefore, is whether the value of new medical technology exceeds its cost. More generally, if new technologies are priced higher than the technologies they replace and consumers value the superior health outcomes that can now be produced, are medical prices rising or falling once one correctly controls for quality? If the government and private health insurers believe new medical technologies are increasing quality-adjusted prices, on average, they may make it more difficult for new products to reach the market and/or reduce payment for new products, which would dampen the financial incentives to innovate. Conversely, if public and private payers believe technology is helping drive down quality-adjusted prices, they are likely to maintain or enhance incentives to innovate.

Berndt et al. (2000) highlight several empirical challenges to measuring medical price

¹Newhouse estimates the proportion of the growth in medical spending accounted for by the aging of the population, improved health insurance based upon the RAND health insurance experiment price elasticity, and rising income based on the RAND income elasticity. Medical technology is the residual once the factors above have been accounted for. Finkelstein (2007) argues that the aggregate, market-wide effects of health insurance on spending are larger than those derived from individual choices in the RAND experiment. She estimates that about one-half of the growth in US hospital spending between 1950 and 1990 was due to the spread of health insurance, which may indicate that medical technology accounts for less than one-half of the growth in medical spending

²Cutler (2004) estimates that two-thirds of this increase was due to changing medical technologies, primarily for the treatment of cardiovascular disease. The remaining one-third was due to behavioral changes.

indexes. Due to health insurance, most consumers do not face the full price of medical care and will seek to consume beyond the point where the marginal value is equal to the full price. Patients also rely on physicians to provide information regarding the value of medical goods and services. The implication is that consumer purchases in the medical market will not necessarily reveal their marginal valuation of a good or service. Perhaps the greatest empirical challenge for constructing meaningful price indexes in health care is how to account for the changing quality of medical products and services.

Due to these considerable empirical challenges, there have been few studies of whether medical prices are rising or falling once one takes into consideration the attributes of the new products and consumers' valuations of those attributes. Cutler et al. (1998) show that the life expectancy of heart attack patients increased by eight months between 1984 and 1991. The value of per-patient expected longevity (\$11,100) increased three times more than treatment costs (\$3,600) during this time period in real terms, which implies that the quality-adjusted price index fell by about one percent annually. Berndt et al. (2002) conclude that the real cost of treating major depression decreased by about two percent per year between 1991 and 1996 once one takes into account the probability that a patient's depression goes into remission.

The pharmaceutical industry is the source of considerable innovation in medical care. The pharmaceutical industry invests over \$30 billion per year in research and development, which represents about 16 percent of the industry's revenue. Most new pharmaceuticals are priced higher than the treatment methods they replace, and this has certainly been the case with colorectal cancer drugs. The average price of providing a colorectal cancer patient with a 24-week chemotherapy drug regimen increased from \$126 in 1993 to over \$20,000 in 2005. There has been substantial innovation in the treatment of colorectal cancer patients over the last decade.³ Five new drugs were approved by the Food and Drug Administration (FDA) for the treatment of colorectal cancer between 1996 and 2004, and these drugs collectively

³13.2 percent of drugs entering Phase 1 trials between 1998 and 2004 were targeting cancer according to the PharmaProjects data base.

had an 86 percent market share by the third quarter of 2005.⁴

We examine whether the substantial increase in spending associated with pharmaceutical innovation in the treatment of colorectal cancer has been worth it. Specifically, we estimate a price index for colorectal cancer drugs for each quarter between 1993 and the first half of 2005 that takes into consideration the quality (i.e., the efficacy and side effects as reported in clinical trials) of each drug on the market and the value that oncologists attach to drug quality.

We estimate a quality-adjusted price index using methods developed by Berry (1994), Berry et al. (1995), Berry and Pakes (2007) and Nevo (2003). These techniques have been used to estimate the welfare effects of new automobiles (Petrin (2002), computers (Pakes (2003), Song (2007), Song (2005)), and breakfast cereal (Nevo (2003))), but few contributions apply them to medical markets. Trajtenberg (1990) focused on the value of innovation on medical devices, specifically CT scanners, and provided various price indices. Cleanthous (2004) and Conti (2006) study the value of innovation for anti-depressants, however, none of them constructs a price index.

The first step in constructing the price index is to estimate oncologists' demand for colon cancer regimens, which we argue is a function of the observed and unobserved quality of each regimen, as well as the price a physician must pay to acquire the regimen. An observation in this estimation is the market share of each regimen for each quarter. The second step is to calculate the equivalent variation (EV) between each adjacent pair of quarters. The EV between period $t - 1$ and t is the change in spending required to achieve physicians' utility in period t relative to $t - 1$, taking into consideration that both the quality of the drug regimens on the market and the prices of those regimens may have changed between these two periods. Positive values imply that the value of the drugs is increasing over time by more than their prices, whereas negative values imply the opposite. The third step is to translate the EV into a quality-adjusted price index by calculating the change in drug prices that is consistent with the welfare effect captured by the EV.

We generate two additional indexes for purposes of comparison. First, we estimate a

⁴Market share data are from IntrinsiQ.

“naive” price index that merely reports the mean price of colon cancer regimens in each quarter, relative to the first quarter of 1993, without any adjustments for regimen attributes. The naive index will be based on the price physicians pay to acquire each regimen, and the market share of each regimen. Comparing the quality-adjusted price index to the naive index illustrates the importance of accounting for the changing quality of pharmaceutical products. Second, we estimate a hedonic price index that is computed by regressing prices on product characteristics and quarter indicator variables. This regression controls to control for changing product attributes by means of a reduced form projection of markups on the characteristic space, and it has been the method traditionally used to account for changing attributes and the introduction of new goods.

The naive price index, which increased by 2600 percent between 1993 and 2005, greatly overestimates the price increase. Both the hedonic price index and the quality-adjusted price index show that prices have actually decreased slightly over the 13-year period we study. The hedonic and quality-adjusted price index are similar during the period without innovation, and both exhibit a decrease when the first branded product is introduced in the market, although the magnitude of that decrease differs between the two indices. For the following period of innovation the two indices show opposite trends, with the hedonic price increasing and the quality-adjusted index decreasing. This discrepancy may be due to the fact that the hedonic price index is less sensitive to “filling the spectrum” or “extending the range” types of innovation (Trajtenberg (1990)), which is the one that seems to occur during this period. Both indices show an increasing trend towards the end of the period, when new and expensive second line drugs are launched, whose efficacy attributes are lower than the existing drugs because they are second line therapies. The levels of the quality-adjusted and hedonic price indices demonstrate that the pricing strategies of pharmaceutical firms allow them to appropriate most of the extra welfare they generate from improved product attributes. All of the new drugs in our sample period are still under patent protection. Presumably consumers would capture more of the surplus once generic drugs enter the market.

2 Overview of Colorectal Cancer

Colorectal cancer is a good health condition for studying the welfare effects of medical innovation because it is a common health condition, the majority of patients today are treated with drugs that did not exist a decade ago, and treatment costs are rising rapidly. According to the National Cancer Institute, approximately 112,000 patients will be diagnosed with colorectal cancer in the United States in 2007, and 52,000 will die from the disease. This places colorectal cancer as the fourth most common cancer based on number of new patients, after breast, prostate, and lung. It is estimated that people born today will have a 5.4 percent chance of being diagnosed with colorectal cancer over their lifetime. The disease is treatable, however; between 1996 and 2003, colorectal cancer patients had a 64 percent chance of surviving for five years.

There are other important reasons we decided to study colorectal cancer treatment. For most health conditions, if a physician writes a prescription for a drug, the patient takes the prescription to a pharmacy, the patient pays a co-payment or co-insurance rate, and the patient's health insurance company pays the balance of the price. By observing the price (co-payment) patients face and their decisions, one could estimate patients' demand for prescription drugs only for a portion of the demand curve, which would make it impossible to estimate consumers' total willingness to pay for a product.

Most oncology drugs are infused into a patient intravenously in a physician's office or an outpatient hospital clinic by a nurse under a physician's supervision.⁵ Unlike drugs that are distributed through pharmacies, physicians (and some hospitals on behalf of their physicians) purchase oncology drugs from wholesalers or distributors (who have previously purchased the drugs from the manufacturers), store the drugs, and administer them as needed to their patients. Physicians then bill the patient's insurance company for an administration fee and the cost of the drug. Although physicians are eventually reimbursed by health insurers, they

⁵Based on data from IMS Health, 59% of colorectal cancer drugs in the third quarter of 2005 were purchased by physician offices/clinics and 28% by hospitals. The remainder was purchased by retail and mail order pharmacies, health maintenance organizations, and long-term care facilities.

do take temporary ownership of oncology drugs. As such, physicians face the possible risk of not being reimbursed by health insurers and may incur substantial carrying costs. For example, a physician who pays \$20,000 for the drugs in a patient's regimen and experiences a three-month delay between when he acquires the drugs and when he is reimbursed by a health insurer would incur an inventory carrying cost of \$533 at an interest rate of eight percent. Because we observe the full price that physicians pay for colorectal cancer drugs, we can estimate physicians' demand for those drugs. If physicians act as agents for their patients, we indirectly observe patients' willingness to pay for these drugs.

Almost all colorectal cancer patients who are treated with pharmaceuticals receive multiple drugs in the form of a regimen rather than a single drug, similar to anti-retroviral "cocktail" treatments for AIDS patients. For example, the regimen with the greatest market share in 2005 contained four separate drugs: bevacizumab, oxaliplatin, fluorororocil, and leucovorin. The 12 regimens in our sample are reported in Table 1. Most of our analysis, therefore, is conducted at the level of a regimen rather than a drug.

3 Empirical Methods

To account for changes in quality of new goods we use a hedonic price regression and the construction of a quality-adjusted price index. The quality-adjusted price index is constructed from the estimated benefits of innovation that were derived from the estimation of a discrete choice model of demand for colon cancer drugs. The technical details of each approach are described in this section.

3.1 Hedonic Price Regression

Hedonic price regressions were introduced by Court (1939) and formalized by Griliches (1961) as a way to account for the new goods problem. In essence, newer goods usually contain more desirable characteristics, and therefore, failing to account for these effects will overstate the true change in prices. The hedonic price regression is motivated by the "hedonic hypothesis," which states that goods can be viewed as aggregations or bundles of lower order variables that

the literature calls characteristics or attributes. These characteristics are the variables that consumers care about and that are present in their utility functions. The hedonic function provides a disaggregation of the observed transaction prices into the variables that affect the economic agents' behavior. Court and Griliches proposed estimating a surface that relates prices to product characteristics and time, and then use the results to obtain estimates of the price changes keeping the characteristics constant.

For our application, we estimate the following hedonic price regression

$$\ln p_{it} = \beta x_{it} + \sum_{t=93:2}^{05:3} \gamma_t d_t + \varepsilon_{it} \quad (1)$$

where p_{it} is the price of regimen i in quarter t , x_{it} contains the attributes of each regimen, including effectiveness attributes such as survival rate, time-to-progression, and response rate, a second line treatment indicator, the interactions between the effectiveness attributes above and the second line indicator, grade 3 or 4 side effects such as diarrhea, nausea, abdominal pain, vomiting and neutropenia, and an indicator of whether the regimen contains a tablet or not. The time dummies denote quarters and the base quarter is the first quarter of 1993.

The change in prices is obtained from the parameters of the time dummies as

$$\frac{PI_t - PI_{t-1}}{PI_{t-1}} = \exp(\gamma_t - \gamma_{t-1}) - 1$$

and therefore,

$$PI_t = \exp(\gamma_t - \gamma_{t-1})PI_{t-1}$$

The parameters β in equation (1) have been referred to as “implicit prices”, however, the theoretical foundations of the hedonic surface are not clear. Pakes (2005) argues that in oligopolistic markets, price is a combination of marginal costs and markups, and therefore the hedonic price regression constitutes a reduced form or projection of these markups on the characteristic space. In the industry we study, given the high costs of R&D relative to marginal cost, markups should be large and Pakes’s insights are applicable. The parameters β do not necessarily follow any restriction based on economic theory. That is, the β parameters may have the “wrong” sign. For example, if there is more entry of products into a particular region of the attribute space that has more desirable characteristics for the average consumer

(e.g., survival), this will reduce the markups of these products, and allow the product with less desirable characteristics for the average consumer (e.g., stronger side effects) to exploit monopoly power among the consumers who do not experience the strong side effects. The results of the hedonic price regression are discussed in the results section of the paper.

3.2 Quality-Adjusted Price Index

We compute a second set of price indices that explicitly calculate the changes in welfare from the introduction of new products. These indexes are derived from the estimation of an equilibrium model of colon cancer drug pricing. Trajtenberg (1990), who introduced the idea, proposed a two-stage method to construct a quality-adjusted price index. In the first stage, the welfare gains from product innovation are obtained, and in the second stage the price index is built upon those welfare gains.

In this paper the first step is performed by estimating a logit model, where the preferences of the physician i over regimens $j \in \{0, \dots, J_t\}$ at time t are represented by the following indirect utility function

$$u_{ijt} = -\alpha p_{jt} + \beta x_{jt} + \xi_j + \Delta\xi_{jt} + \varepsilon_{ijt}$$

where p_{jt} is the price of regimen j at time t , x_{jt} are the observable attributes of the regimen, ξ_j is the mean of the unobserved characteristics, and $\Delta\xi_{jt}$ is a time-specific deviation from this mean. ε_{ijt} , which is an idiosyncratic shock to preferences for regimen j , is assumed to follow a Type I Extreme Value distribution.⁶ The outside option ($j = 0$) in this paper includes off-label colon cancer treatments and regimens with very small market shares for which a complete set of is not observed.

⁶In this model all the individual-specific heterogeneity is contained in the idiosyncratic shock to preferences, and therefore, it suffers from the well-known independence of irrelevant alternatives criticism (see Nevo (2000) for a complete discussion of the limitations of this approach). In addition, Petrin (2002) points out that the welfare calculations based on these models depend heavily on the error term. We are currently estimating more flexible specifications such as the ones proposed by Berry et al. (1995), and the pure characteristics approach proposed in Berry and Pakes (2007)

Patients are assumed to be administered one regimen at a given time, which maximizes their utility. This implicitly defines a region of the unobserved term for which alternative j yields a higher utility than any other alternative k

$$A_{jt} = \{\varepsilon_{it} | u_{ijt} \geq u_{ikt} \forall k \neq j\}$$

The market shares for each regimen j can be obtained by aggregating the individual preferences over the region A_{jt}

$$\sigma_{jt} = \int_{A_{jt}} dP(\varepsilon)$$

If ε is assumed to be drawn from the extreme value distribution, the integral can be computed analytically:

$$\sigma_{jt} = \frac{\exp(-\alpha p_{jt} + \beta x_{jt} + \xi_j + \Delta\xi_j)}{1 + \sum_{k=1}^{J_t} \exp(-\alpha p_{kt} + \beta x_{kt} + \xi_k + \Delta\xi_k)}$$

We define the mean utility level $\delta_{jt} = -\alpha p_{jt} + \beta x_{jt} + \xi_j + \Delta\xi_j$, and therefore, the market shares can be written as the function $\sigma_{jt}(\delta_t)$, with δ_t being the vector of mean utilities at time t .

The market shares predicted by the model $\sigma_{jt}(\delta_t)$ are then matched with the observed market shares s_{jt} . Berry (1994) shows that δ_j can be uniquely identified by inverting the market share function $\sigma^{-1}(s_t) = \delta_t$. For the logit model, the inversion yields

$$\ln s_{jt} - \ln s_{0t} = -\alpha p_{jt} + \beta x_{jt} + \xi_j + \Delta\xi_j$$

Because the unobserved drug regimen characteristics are likely to be correlated with price, the estimation of the equation above requires the use of instrumental variables. We obtain our instruments by using the supply side market equilibrium conditions. Specifically, we assume that firms play a static Nash-Bertrand game, and for the regimens that combine drugs from different companies, we assume the surplus is divided proportionally.⁷ Because price is a function of marginal cost and markups, any exogenous variable that shifts marginal costs or

⁷Work in progress relaxes this assumption.

markups is a good instrument. We follow Bresnahan et al. (1997) and use the number of products in the market and the sum of observed characteristics of the competitors (which the literature assumes as exogenous and provides a sense of how crowded is the product space) as our instruments. Both sets of instruments will shift markups through changes in the competitive environment, and therefore, will be correlated with price, but uncorrelated with the unobserved characteristics.

The price index is built based on the changes in compensating variation derived from the estimation of the model described above. The compensating variation provides a measure of how much income could be taken away from (or given to) an individual and leave him indifferent between facing the old choice set and the new improved (inferior) choice set. Given the logit functional form assumption, the compensating variation is calculated as

$$CV_t = \frac{u_t - u_{t-1}}{\alpha}$$

where u_t is the unconditional indirect utility $u_t = \max_j u_{jt}$ and α is the marginal utility of income. Small and Rosen (1981) show that u_t can be computed as

$$u_t = \ln \sum_j \exp(\delta_j)$$

Trajtenberg (1990) shows that if the price change takes the form of a shift by a factor of $(1 - \mu_t)$ in the distribution of prices but the variance remains the same, then the price index can be obtained as

$$PI_t = (1 - \mu_t)PI_{t-1}$$

where

$$\mu_t = \frac{CV_t}{CV_t + \bar{p}_t}$$

and \bar{p}_t is the average price in period t .

4 Data

We use a number of different data sources to collect four types of information: drug prices, regimen market shares, typical drug dosage amounts for each regimen, and regimen attributes.

IMS Health collects information on the sales in dollars and the quantity of drugs purchased by 10 different types of customers (e.g., hospitals, physician offices, retail pharmacies) from wholesalers in each quarter from 1993 through the third quarter of 2005. Prices and quantities are reported separately by National Drug Classification (NDC) code, which are unique for each firm-product-strength/dosage-package size. We calculate the average price paid per milligram of active ingredient of a drug by averaging across the different NDC codes for that drug. IMS Health reports the invoice price a customer actually pays to a wholesaler, not the average wholesale price (AWP) that is set by a manufacturer and often differs substantially from the true transaction price.

The price we calculate does not include any discounts or rebates a customer may receive from a manufacturer after purchasing the product from the wholesaler. Based on interviews with a few oncologists, we do not believe that manufacturers offered substantial rebates during this period. Although we have information on 10 different types of customers, we focus on the prices paid by the two largest customers - hospitals and physician offices. Because most oncology drugs are infused in a physician's office or hospital clinic, nursing homes and retail pharmacies purchase relatively little.

Most colon cancer patients are treated with regimens that combine two or more drugs. The IMS Health data contain information on market share by drug, but not market share for the combinations of drugs (regimens) actually used on patients. We rely, therefore, on two different sources for regimen-specific market shares. IntrinsiQ is a company that surveys a nationally representative group of oncologists monthly and asks them extensive questions regarding how they currently treat cancer patients. IntrinsiQ provided data on the proportion of colorectal cancer patients (of all ages) treated with chemotherapy who are treated with each regimen for each month between January 2002 and September 2005.⁸

⁸Because we observe the market shares of regimens among patients with colorectal cancer, we do not need to worry about off-label use. Off-label use occurs when a physician treats a colorectal cancer patient with a drug that has not been approved by the FDA to treat colorectal cancer, or when a physician uses a drug approved for colorectal cancer on a patient with a different type of cancer. In October 2005, seventy-six percent of patients being treated with the four drugs approved solely for the treatment of colorectal cancer (irinotecan, oxaliplatin, cetuximab, and bevacizumab) actually had colorectal cancer. That is, off-label use

We derive market shares for the 1993 to 2001 period from the Surveillance Epidemiology and End Results (SEER) data set, which tracks the health and treatment of cancer patients over the age of 64 in states and cities covering 26 percent of the United States population.⁹ We calculate the proportion of colorectal cancer patients who are treated with each drug regimen in each quarter based on Medicare claims data available in SEER. In October 2003, approximately 48 percent of all colorectal cancer patients treated with chemotherapy were 65 years or older.¹⁰

In the 1993 to 2001 period, when there were relatively few treatment options for colorectal cancer, we include all regimens that contain drugs that were explicitly approved by the Food and Drug Administration (FDA) for colorectal cancer and had a market share greater than two percent. Market shares of all other drugs are combined into an outside option, which in this early period will consist primarily of off-label drugs - drugs approved for conditions other than colorectal cancer that are used on colorectal cancer patients.¹¹ In the 2002 to 2005 period, the outside option includes off-label drugs, regimens with less than one percent market share in the third quarter of 2005 (the end of the sample period), and regimens with missing attribute data.

Market shares for the 12 regimens in our sample and the outside option are plotted in Figure 1. The regimens are also described more fully in Table 1, arranged in order of entry. Between 1993 and 1996, about 80 percent of colorectal cancer patients were treated with 5-FU/leucovorin, which at that time was generic, with the remainder treated with off-label drugs or regimens with very small market share.¹² Irinotecan (brand name Camptosar) was approved by the FDA for treating colorectal cancer in 1996, and over the next several years the market share of irinotecan and irinotecan combined with 5-FU/LV grew at the expense of 5-FU/LV.¹³ Capecitabine (Xeloda), a tablet that produces the same chemical response as

⁹SEER contains data on the incidence rate of cancer among the non-elderly, but only has medical claims available for Medicare patients.

¹⁰Data from IntrinsicQ.

¹¹Off-label use is more likely to occur if a patient's initial treatment has been unsuccessful.

¹²5-FU contains the drug fluorororacil.

¹³Because it takes Medicare a while to code new drugs into their proper NDC code, for several quarters a

5-FU/LV, was approved for treatment of colorectal cancer in 1998 and was administered as a standalone therapy or combined with irinotecan. The market share of capecitabine was quite small initially.¹⁴ All other drugs for treating colorectal cancer in our sample are delivered intravenously (IV) under the supervision of a physician or nurse.

Oxaliplatin (Eloxatin) was introduced in 2002, followed by cetuximab (Erbix) and bevacizumab (Avastin) in 2004. By the third quarter of 2005, two of the regimens created by these three new drugs (oxaliplatin + 5-FU/LV and bevacizumab + oxaliplatin + 5-FU/LV) surpassed the market share of 5-FU/LV, whose share had fallen to about 14 percent.

The market shares of several regimens change sharply in the first quarter of 2002 when we collect market shares from IntrinsiQ rather than SEER. One explanation for these changes is that Medicare patients may be treated with different regimens than non-Medicare patients. In a future version of the paper we plan to apply a regimen-specific factor to adjust the pre-2002 market shares based on the ratio of total (from IntrinsiQ) to Medicare-only (from SEER) market shares for the 2002 when the two data sets overlap. Another explanation is that the samples used by IntrinsiQ and/or SEER may not be consistent.¹⁵

In order to calculate the price per regimen, we require information on the quantity of each drug in a regimen. The National Comprehensive Cancer Network (NCCN) reports the typical amount of active ingredient used by physicians for the major regimens. We supplement this where necessary with dosage information from drug package inserts, conference abstracts, and journal articles. Dosage information is reported in Appendix 1. For example, the standard dosage schedule for the regimen with the second largest market share in 2005 is 85 milligrams (mg) of oxaliplatin per meter squared of a patient's surface area infused by IV on the first day of treatment, followed by a 1,000 mg infusion of 5-FU per meter squared of surface area on the first and second treatment days, and a 200 mg infusion of leucovorin per meter squared on the first and second treatment days. This process is repeated every two weeks. We price the

new drug will appear in the outside option.

¹⁴Because capecitabine is not covered by Medicare Part B, unlike the IV-administered drugs, the Medicare claims data are likely to underestimate its use. This is not an issue in the IntrinsiQ data, which are collected by surveying physicians.

¹⁵The SEER sample is drawn from locations representing 26 percent of the U.S. population.

regimens for a representative patient who has 1.7 meters squared of surface area (Jacobson et al., 2006) weighs 80 kilograms, and is treated for 24 weeks. Regimen prices are derived by multiplying the average price a customer paid per milligram of active ingredient in a quarter by the recommended dosage amounts for each drug in the regimen over a 24-week period.¹⁶

We obtain most of the attribute information for each regimen from the FDA-approved package inserts that accompany each drug. These inserts describe the phase 3 clinical trials that were conducted, including the number and types of patients enrolled in the trials, the health outcomes for patients in the treatment and control groups, and the side effects experienced by those patients. Often there are multiple observations for a regimen, either because a manufacturer conducted separate trials of the same regimen, or because a regimen may have been the treatment group in one clinical trial and the control group in a subsequent trial. In these cases we calculate the mean attributes across the separate observations. Where necessary, we supplement the package insert information with abstracts presented at oncology conferences and journal articles.

The attribute information is summarized in Table 1, organized according to the year when each regimen was introduced. We record three measures of a regimen's efficacy: the median number of months patients survive after initiating therapy; the percentage of patients who experience a substantial reduction in the size of their tumor; and the mean number of months (across patients in the trial) before their cancer advanced to a more serious stage.¹⁷ For all three of these measures, higher values are associated with superior health outcomes. We also record whether a regimen contains the capecitabine tablet, which should make the administration of the regimen more convenient for a patient, and whether the regimen is approved (and was tested) as a second line treatment. Efficacy measures for second-line regimens will generally be worse than those for first-line regimens because the patients' cancer is likely to be more advanced at the beginning of the clinical trial and the first treatment was not completely successful.

¹⁶The regimens are priced used price data for the contemporaneous quarter only.

¹⁷Cancers are classified into four stages, with higher numbers indicating that the cancer has metastasized beyond its initial location.

We also collected data on the percentage of patients in phase 3 trials who experienced either a grade 3 or a grade 4 side effect for five separate conditions: abdominal pain, diarrhea, nausea, vomiting, and neutropenia. Although many more side effects are recorded for most regimens, these five were consistently recorded across the 12 regimens in the sample. Side effects are classified on a standard one to four scale, with four being the most severe. Higher values for the side effect attributes should be associated with worse health outcomes although, as we will show later, regimens that are more toxic are likely to be both more effective and have more severe side effects.

New colorectal cancer regimens tend to be more efficacious than the existing regimens, with side effect profiles that are sometimes more and sometimes less severe than earlier regimens. Consider the new entrant in 1996, irinotecan + 5-FU/LV (third row of Table 1). Relative to patients who received 5-FU/LV in a clinical trial (first row of Table 1), patients in clinical trials who received irinotecan + 5-FU/LV lived 3.1 months longer, on average, had a 14.6 percentage point higher probability of experiencing a reduction in the size of their tumor, and experienced a two month delay in the time it took for the cancer to advance to a more severe stage. However, patients taking the new regimen were more likely to experience four of the five side effects listed in Table 1.

Oxaliplatin + 5-FU/LV, which was launched in 2002 (sixth row of Table 1), is more efficacious and has fewer severe side effects than irinotecan + 5-FU/LV. Patients in clinical trials of the former regimen lived an average of 3.8 months longer, had a 10.7 percentage point higher probability of experiencing a reduction in the size of their tumor, and experienced a 2.4 month delay in the time it took for the cancer to advance to a more severe stage relative to the latter regimen. Oxaliplatin + 5-FU/LV patients are also less likely to experience a grade 3 or 4 side effect for four of the five measures relative to irinotecan + 5-FU/LV. Finally, the arrival of bevacizumab + irinotecan + 5-FU in 2004 increased the median survival time by about one month relative to oxaliplatin + 5-FU/LV, with substantial improvements on three side effect measures and worse performance on the other two side effect measures.

There has been one situation where a new second-line regimen entered the market after

another second-line regimen.¹⁸ Bevacizumab + oxaliplatin + 5-FU/LV had a substantially better response rate and time-to-progression performance than the two cetuximab-based regimens that beat it to the market by a matter of months in 2004. The new regimen had a mixed side effect profile relative to the cetuximab-based regimens.

5 Results

In Figure 2 we plot the mean regimen price by quarter by multiplying the market share of each regimen by the price physicians paid for that regimen. Since we do not observe prices for the outside option, regimen market shares are rescaled to equal one once the outside option is omitted. The price to physicians of a 24-week 5-FU/LV regimen in the first quarter of 1993 was \$126. The mean price of colorectal cancer drugs increased to \$1,839 in the first quarter of 1998 when two new irinotecan-based regimens first appeared in the SEER data set.¹⁹ In the first quarter of 1998, physicians paid \$16,806 for a 24-week regimen of irinotecan and \$15,944 for a 24-week regimen of irinotecan + 5-FU/LV. Mean prices rose sharply between 1998 and 2001 as the market share of the irinotecan-based regimens increased and capecitabine was launched (see Figure 2). Most of the increase was due to patients being shifted to the irinotecan-based regimens (see Figure 1) rather than increases in the prices of the new regimens once they were launched. The mean regimen price increased by 483 percent between the first quarter of 1998 and the first quarter of 2001, whereas the prices of the two irinotecan-based regimens increased by 24 percent and 22 percent during the same time period.

The mean regimen price increased from \$8,539 in the third quarter of 2002 to \$12,527 in the third quarter of 2003 (a 47 percent annual increase), to \$26,826 in the third quarter of 2004 (a 114 percent increase from 2003), and finally to \$36,305 in the third quarter of 2005 (a 35 percent increase from 2004). The prices of the three regimens with the largest market

¹⁸Regimens that include the tablet, capecitabine, are chemically equivalent to regimens that include 5-FU/LV.

¹⁹Irinotecan began generating sales in the IMS Health data set in the second quarter of 1996. However, Medicare claims recorded irinotecan in an "other" category until the first quarter of 1998.

share in the third quarter of 2005 were bevacizumab + oxaliplatin + 5-FU (price of \$76,636 and 18.9 percent market share), oxaliplatin + 5-FU/LV (price of \$25,400 and 17.8 percent market share), and 5-FU/LV (price of \$75 and 13.6 percent market share). The first of these three is a second-line therapy.

To derive a naive price index that does not account for the changing attributes of the regimens, we divide the mean prices in Figure 1 by \$126, the mean price in the first quarter of 1993. The shape of the naive index is identical to that of Figure 1, with the only difference that it is indexed to one in the first quarter of 1993 and reaches 286 in the third quarter of 2005. Prices increased by 28,600 percent between the first quarter of 1993 and the third quarter of 2005.

Coefficient estimates from the hedonic regression are reported in Table 2. The dependent variable is the logarithm of the price a customer paid for regimen j in quarter t . Regimen attributes are included as well as a full set of quarter indicator variables. We also interact the second line therapy indicator with a regimen's response rate.²⁰

The coefficients on two of the three efficacy measures are positive and significant. An increase of one month in the median patient survival is associated with a 64.2 percent increase in the price of a regimen.²¹ Evaluated at the mean regimen price in the sample (\$21,113), this implies an increase of \$13,555. Physicians are implicitly valuing an expected year of life saved at \$162,700. Regimens with relatively high response rates are also priced higher, with the effect smaller for second-line therapies.

The coefficient on time to progression is negative, which seems to indicate that physicians assign a negative valuation to that attribute. Pakes (2005) shows that coefficients in hedonic regressions will not necessarily have their expected signs. His insight is that the degree of competition will differ across the attribute space. In the situation of colorectal cancer, for example, there may be greater differentiation and less competition with the survival and response rate attributes relative to time to progression. Pharmaceutical and biotech firms design their products and construct the clinical trials that will define the attributes years

²⁰We did not include other second-line attribute interactions due to multi-colinearity.

²¹ $0.642 = \exp(0.496) - 1$.

before the products are approved and marketed. It is quite plausible, therefore, that at any given point in time there could be more differentiation on certain attributes than others.

Two of the side effect attributes have negative coefficients and three have positive coefficients in Table 2. Cancer patients often take drugs that ameliorate the impact of certain side effects, such as pain, nausea, and vomiting. In addition to the explanation above, this may be another reason why physicians seem to assign a positive value to the abdominal pain, nausea, and vomiting side effects. If a physician prescribes anti-pain and antiemetic drugs in conjunction with the anti-cancer drugs, she may downgrade the importance of these side effects when choosing a regimen. A third possible explanation for the positive coefficients on three of the side effect attributes is that physicians may believe that the efficacy of the newer drugs are better than the measures reported in phase 3 clinical trials. This could occur, for example, if physicians use the drugs differently in practice than as they were used in the trials due to learning about patient-drug matching. Because the newer drugs are more toxic and generally have greater side effects, the physician beliefs would be captured as positive coefficients on the side effect measures.

The very large positive coefficient on the second-line indicator variable confirms that these therapies are priced much higher than first-line therapies, controlling for the attributes of each. This implies there is a much higher willingness to pay for an extra life year for the very sick relative to the less sick. Finally, regimens containing the capecitabine tablet are priced slightly lower than regimens that use 5-FU/LV instead. This does not necessarily imply that physicians do not value the convenience associated with the tablet but also less dosage of other drugs. As indicated in Appendix 1, the dosages of certain branded drugs (e.g., irinotecan) are lower when capecitabine is used instead of 5-FU/LV.

We exponentiate the coefficients on the quarter indicator variables (the first quarter of 1993 is omitted) and plot the hedonic price index in Figure 3. The pattern of prices for the hedonic index (the lower line) in Figure 3 is dramatically different from Figure 2, which emphasizes the importance of controlling for product attributes. Prices were stable in nominal terms between 1993 and the second quarter of 1996 when the only regimen approved for colorectal cancer treatment was 5-FU/LV and the components of this regimen were no longer

patent protected. The hedonic index drops by about 25 percentage points with the introduction of the two irinotecan-based therapies, which were priced at about \$16,000. Controlling for the attributes of these new regimens and physicians' valuations of those attributes, prices fell by about 25 percent. Over the next six years, including the period when capecitabine was introduced, the index increased from 0.70 to 0.83, or 18.4 percent. The price index jumped by eight percentage points with the introduction of the oxaliplatin-based regimens in 2002, and has decreased slightly since then during the time when cetuximab and bevacizumab were launched.

In the same figure we show the quality-adjusted price index (the upper line). The quality-adjusted index is very similar to the hedonic price index during the period where only 5-FU/LV was present. There is a decrease of 9 percentage points during 1998, when irinotecan started showing positive market shares.²² That decrease after the introduction of irinotecan was also present in the hedonic price index in 1996, but much more pronounced. During the period 1999 to 2001, the quality-adjusted price index remains fairly constant, even though capecitabine is introduced. During this period the hedonic price index shows a considerable increase that extends towards 2002 when oxaliplatin is introduced. On the other hand, the quality-adjusted index exhibits a decrease after oxaliplatin is introduced, which may provide evidence that the hedonic price index is not able to capture the extending the range or filling the spectrum type of innovation that occurred during this period.²³ The 5-percentage point decrease in the quality-adjusted price index after the introduction of oxaliplatin contrasts with the 8 percentage points increase in the hedonic price index. Finally, the quality-adjusted price index shows a sharp increase after the new second line therapies are introduced.

²²Although irinotecan was introduced in 1996, the SEER data set only shows positive market shares for this drug in 1998.

²³The sharp decline of the quality-adjusted price index in 2002 corresponds to a change of data source for the market shares of the regimens. However, it remains true that the index dropped 5 percentage points when oxaliplatin was introduced.

6 Conclusion

This paper provides evidence to support the idea that new medical technology, in particular colon cancer drugs, provide welfare increases that justify their cost. We calculate a naive price index that does not adjust for improving attributes and compare it with a hedonic price index and a quality-adjusted price index. The conclusions about the evolution of prices of new pharmaceutical developments differs substantially between the naive price index and the two methods that take into account changing product attributes. While the naive price index shows a dramatic increase in prices over the 13-year period we study, the hedonic price and the quality-adjusted price index show slight decreases. The levels of the hedonic and quality-adjusted price indices suggest that pharmaceutical companies are able to capture most of the welfare they generate with the launches of new and better products. Ongoing research will refine these estimates using frontier discrete choice methods for demand estimation.

References

- Berndt, E. R., Bir, A., Busch, S. H., Frank, R. G., , and Normand, S.-L. T. (2002). The medical treatment of depression, 1991-1996: Productive inefficiency, expected outcome variations, and price indexes. *Journal of Health Economics*, 3(21):373–396.
- Berndt, E. R., Cutler, D. M., Frank, R. G., Griliches, Z., Newhouse, J. P., and Triplett, J. E. (2000). *Handbook of Health Economics*, chapter Medical Care Prices and Output. Elsevier Science.
- Berry, S. T. (1994). Estimating discrete-choice models of product differentiation. *Rand Journal of Economics*, 25(2):242–262.
- Berry, S. T., Levinsohn, J., and Pakes, A. (1995). Automobile prices in market equilibrium. *Econometrica*, 63(4):841–890.
- Berry, S. T. and Pakes, A. (2007). The pure characteristics demand model. Working paper, Harvard University.
- Bresnahan, T. F., Stern, S., and Trajtenberg, M. (1997). Market segmentation and the sources of rents from innovation: personal computers in the late 1980s. *RAND Journal of Economics*, 28(0):S17–S44.
- Cleanthous, P. (2004). *Evaluating Innovation in the Pharmaceutical Industry*. PhD thesis, Yale University.
- Conti, R. M. (2006). *The Economic Value of New Treatments for Depression*. PhD thesis, Harvard University.
- Court, A. (1939). *The dynamics of automobile demand*, chapter Hedonice Price Indexes with Automotive examples, pages 99–117. General Motors Corporation.
- Cutler, D. M. (2004). *Your Money or Your Life: Strong Medicine for Americans Health Care System*. Oxford University Press.

- Cutler, D. M., McClellan, M., Newhouse, J. P., and Remler, D. (1998). Are medical prices declining? evidence from heart attack treatments. *The Quarterly Journal of Economics*, 63(4):991–1024.
- Finkelstein, A. (2007). The aggregate effects of health insurance: Evidence from the introduction of medicare. *Quarterly Journal of Economics*, 122(1):1–37.
- Griliches, Z. (1961). *The price statistics of the Federal Government*, chapter Hedonic price indexes for automobiles: an econometric analysis of quality change, pages 173–196. National Bureau of Economic Research.
- Murphy, K. M. and Topel, R. H. (2006). The value of health and longevity. *Journal of Political Economy*, 114(5):871–904.
- Nevo, A. (2000). A practitioner’s guide to estimation of random coefficient logit models of demand. *Journal of Economics & Management Strategy*, 4(9):513–548.
- Nevo, A. (2003). New products, quality changes and welfare measures computed from estimated demand systems. *The Review of Economics and Statistics*, 85(2):266–275.
- Newhouse, J. (1992). Medical care costs: How much welfare loss? *Journal of Economic Perspectives*, 6(3):3–21.
- Pakes, A. (2003). A reconsideration of hedonic price indexes with an application to pc’s. *The American Economic Review*, 93(5):1578–1596.
- Pakes, A. (2005). Hedonics and the consumer price index. Working Paper, Harvard University.
- Petrin, A. (2002). Quantifying the benefits of new products: The case of the minivan. *Journal of Political Economy*, 110(4):705–729.
- Small, K. and Rosen, H. (1981). Applied welfare economics with discrete choice models. *Econometrica*, 49(1):105–130.

- Song, M. (2005). The quality-adjusted price index and consumer heterogeneity. Working paper, Georgia Institute of Technology.
- Song, M. (2007). Measuring consumer welfare in the cpu market: An application of the pure characteristics demand model. forthcoming *RAND Journal of Economics*.
- Trajtenberg, M. (1990). Product innovations, price indices and the (mis)measurement of economic performance. Working paper, NBER 3261.

Table 1: Attributes of the Drug Regimens

<u>Regimen</u>	<u>Year Launched</u>	<u>Efficacy Measures</u>			<u>Grade 3 or Grade 4 Side Effects</u>				
		<u>Survival Months</u>	<u>Response Rate</u>	<u>Time to Progression</u>	<u>Abdominal Pain</u>	<u>Diarrhea</u>	<u>Nausea</u>	<u>Vomiting</u>	<u>Neutropenia</u>
First-line therapies									
5-FU + Leucovorin	1991	12.5	20.8	4.7	5.5	10.4	4.8	4.4	33.7
Irinotecan (Camptosar)	1996	12.0	18.0	4.2	13.0	31.0	16.1	12.1	31.4
Irinotecan + 5-FU/LV	1996	15.6	35.4	6.7	5.3	24.0	11.9	8.0	39.5
Capecitabine (Xeloda)	1998	13.1	21.0	4.4	9.5	15.0	4.0	4.5	3.0
Irinotecan + capecitabine	1998	15.6	35.4	6.7	5.3	24.0	11.9	8.0	39.5
Oxaliplatin (Eloxatin) + 5-FU/LV	2002	19.4	46.1	9.1	6.0	15.4	4.4	5.5	38.8
Oxaliplatin + capecitabine	2002	18.0	36.5	8.1	6.0	21.9	15.6	11.3	3.7
Bevacizumab + irinotecan + 5-FU/LV	2004	20.3	45.0	10.6	8.0	34.0	1.0	1.0	21.0
Second-line therapies									
Cetuximab (Erbix)	2004	N/A	10.8	1.5	9.0	2.0	2.0	3.0	5.0
Cetuximab + irinotecan	2004	N/A	22.9	4.1	8.0	22.0	6.0	7.0	5.0
Bevacizumab (Avastin) + oxaliplatin + 5-FU/LV	2004	12.7	26.9	7.6	8.0	23.1	7.9	8.6	12.2
Bevacizumab + oxaliplatin + capecitabine	2004	12.7	26.9	7.6	8.0	23.1	7.9	19.0	12.0

Notes: the brand name of a drug appears in parentheses in the first column. All attribute information is based on the experiences of patients in clinical trials, usually Phase 3 trials. The median survival is measured in months. Cetuximab was approved without demonstrating a longer survival, and therefore survival is coded as not available (N/A). Response rate is the percentage of patients whose tumor shrunk substantially. Time to progression is the mean number of months for a tumor to advance to a more severe stage, such as from Stage 2 to Stage 3. Second line therapies are approved by the FDA to be used on patients who have been treated previously with a different therapy. The final five columns measure the percentage of patients who experience a grade 3 or grade 4 (on a 1-4 scale, where 4 is the most severe) side effect of a particular type

Table 2

Coefficient Estimates from Hedonic Regression

	<u>Coefficient</u>	<u>Standard Error</u>
Efficacy measures:		
General survival (months)	0.496**	0.0049
Response rate (percentage)	0.422**	0.0027
Response rate * second line indicator	-0.141**	0.0013
Time to progression (months)	-2.58**	0.019
Grade 3 or 4 side effects:		
Diarrhea	0.124**	0.0011
Nausea	0.059**	0.0012
Abdominal pain	0.336**	0.0028
Vomiting	-0.019**	0.0009
Neutropenia	-0.045**	0.0005
Second-line therapy	10.2**	0.050
Tablet	-0.101**	0.0086
Physician clinics (hospitals omitted)	0.0099	0.0093
Constant	-2.18**	0.056
Observations	492	
R ²	0.99	

Notes: the unit of observation is the logarithm of the mean price a type of customer (physician clinics or hospitals) pays for a regimen in a quarter. The regressions include a full set of quarter indicator variables. The interaction between general survival and the second line therapy indicator, and time to progression and the second line therapy indicator are dropped due to colinearity. ** = significantly different from zero at the 5-percent level.

Table 3

	<u>Coefficient</u>	<u>Standard Error</u>
Price	-0.706**	0.079
Efficacy measures:		
General survival (months)	0.248**	0.0085
Response rate (percentage)	0.208**	0.051
Response rate * second line therapy	0.118**	0.031
Time to progression (months)	-0.945**	0.338
Grade 3 or 4 side effects:		
Diarrhea	-0.0015	0.021
Nausea	0.129**	0.0047
Abdominal pain	0.188**	0.0088
Vomiting	-0.010*	0.057
Neutropenia	-0.043**	0.012
Tablet	-2.26**	0.313
Constant	2.26**	0.613
Observations	216	
R ²	0.75	

Notes: the unit of observation is the logarithm of the market share of a regimen in a quarter minus the logarithm of the market share of the outside option. The price variable measures the price that physician clinics paid, on average, to wholesalers for a regimen in a quarter. The regressions include a full set of quarter indicator variables. ** = significantly different from zero at the 5-percent level; * = significantly different from zero at the 1-percent level.

Appendix: Composition and Dosages of the Chemotherapy Regimen

Regimen	1 st Drug	2 nd Drug	3 rd Drug	4 th Drug
5-FU + Leucovorin ²⁰	425 mg of 5-FU/m ² /day for days 1-5, every 4 weeks	20 mg of Leucovorin/m ² /day for days 1-5, every 4 weeks		
Irinotecan	125 mg of irinotecan per week/m ² for 4 weeks, every 6 weeks			
Irinotecan + 5-FU/LV ²¹	180 mg of irinotecan/m ² on day 1, every 2 weeks	1,000 mg of 5-FU/m ² on day 1 and 2, every 2 weeks	400 mg of Leucovorin/m ² on day 1 and day 2, every 2 weeks	
Capecitabine	2,500 mg of capecitabine per m ² /day for days 1-14, every 3 weeks			
Capecitabine + irinotecan	70 mg of irinotecan/m ² /week, every 6 weeks	2,000 mg of capecitabine per m ² /day for days 1-14, every 3 weeks		
Oxaliplatin + 5-FU/LV ²²	85 mg of oxaliplatin per m ² on day 1, every 2 weeks	1,000 mg of 5-FU/m ² on day 1 and day 2, every 2 weeks	200 mg of Leucovorin/m ² on day 1 and day 2, every 2 weeks	
Oxaliplatin + capecitabine	130 mg of oxaliplatin per m ² on day 1, every 3 weeks	1,700 mg of capecitabine per m ² /day for days 1-14, every 3 weeks		
Cetuximab	400 mg of cetuximab per m ² on day 1; then 250 mg/m ² once a week, every 6 weeks			
Cetuximab + irinotecan	400 mg of cetuximab per m ² on day 1; then 250 mg/m ² once a week, every 6 weeks	125 mg of irinotecan per week/m ² for 4 weeks, every 6 weeks		

²⁰ Mayo treatment method.

²¹ FOLFIRI treatment method.

²² FOLFOX treatment method.

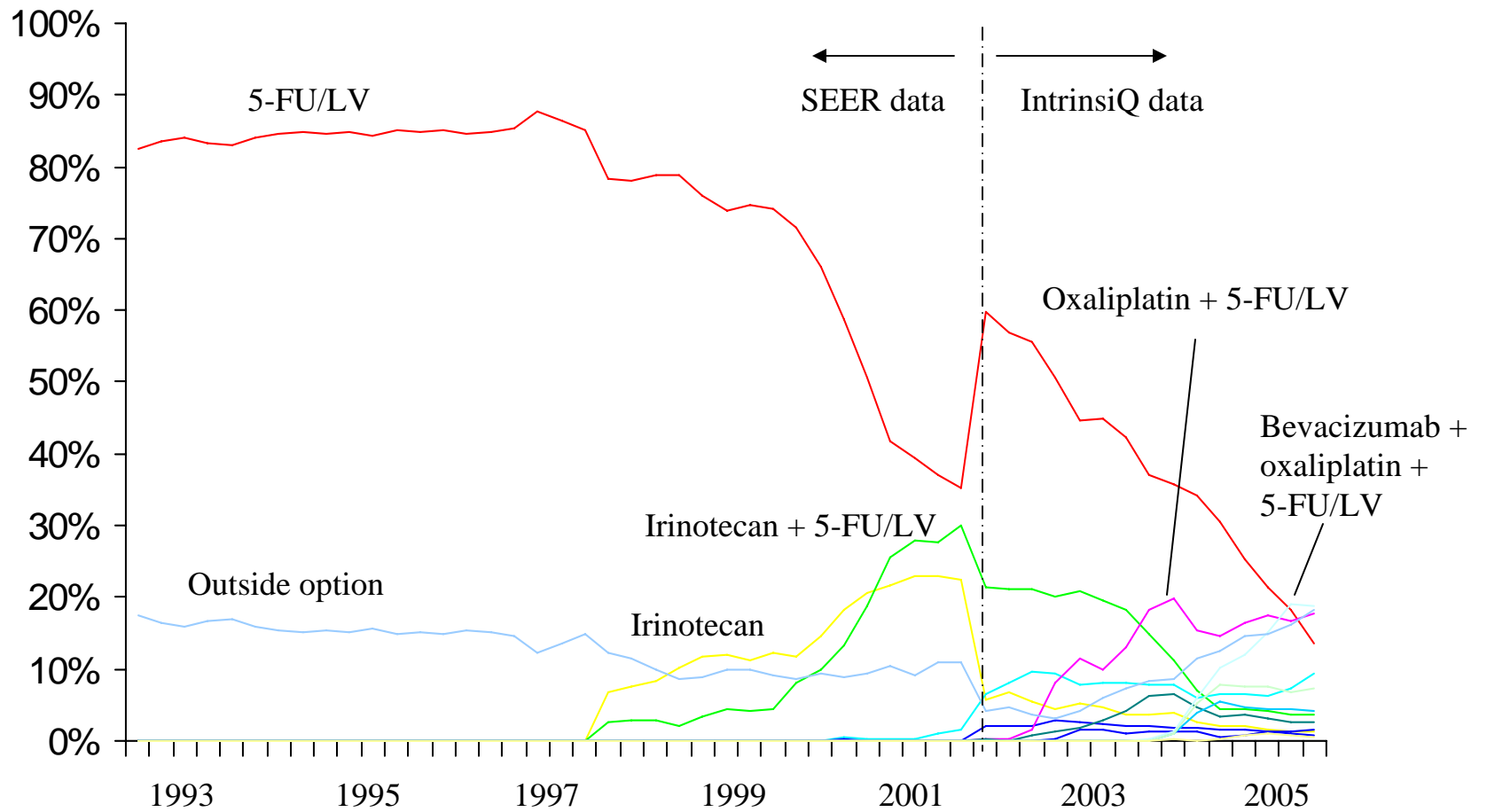
	6 weeks			
Bevacizumab + oxaliplatin + 5-FU/LV	5 mg of bevacizumab per kg, every 2 weeks	85 mg of oxaliplatin per m ² on day 1, every 2 weeks	1,000 mg of 5-FU/m ² on day 1 and day 2, every 2 weeks	200 mg of Leucovorin/m ² on day 1 and day 2, every 2 weeks
Bevacizumab + irinotecan + 5-FU/LV	5 mg of bevacizumab per kg, every 2 weeks	180 mg of irinotecan/m ² on day 1, every 2 weeks	1,000 mg of 5-FU/m ² on day 1 and 2, every 2 weeks	400 mg of Leucovorin/m ² on day 1 and day 2, every 2 weeks
Bevacizumab + oxaliplatin + capecitabine ²³	7.5 mg of bevacizumab per kg, every 3 weeks	130 mg of irinotecan/m ² on day 1, every 3 weeks	1,700 mg of capecitabine per m ² /day for days 1-14, every 3 weeks	

Notes: each regimen is assumed to last for 24 weeks. The four-week 5-FU + Leucovorin regimen, for example, is assumed to be repeated six times during a patient's treatment cycle. mg = milligram of active ingredient; m² = meter squared of a patient's surface area; kg = kilogram of a patient's weight. We price the regimens for a patient who has a surface area of 1.7 m² and weighs 80 kilograms.

Source: National Comprehensive Cancer Network, Colon Cancer, Version 2.2006; package inserts.

²³ CAPOX treatment method.

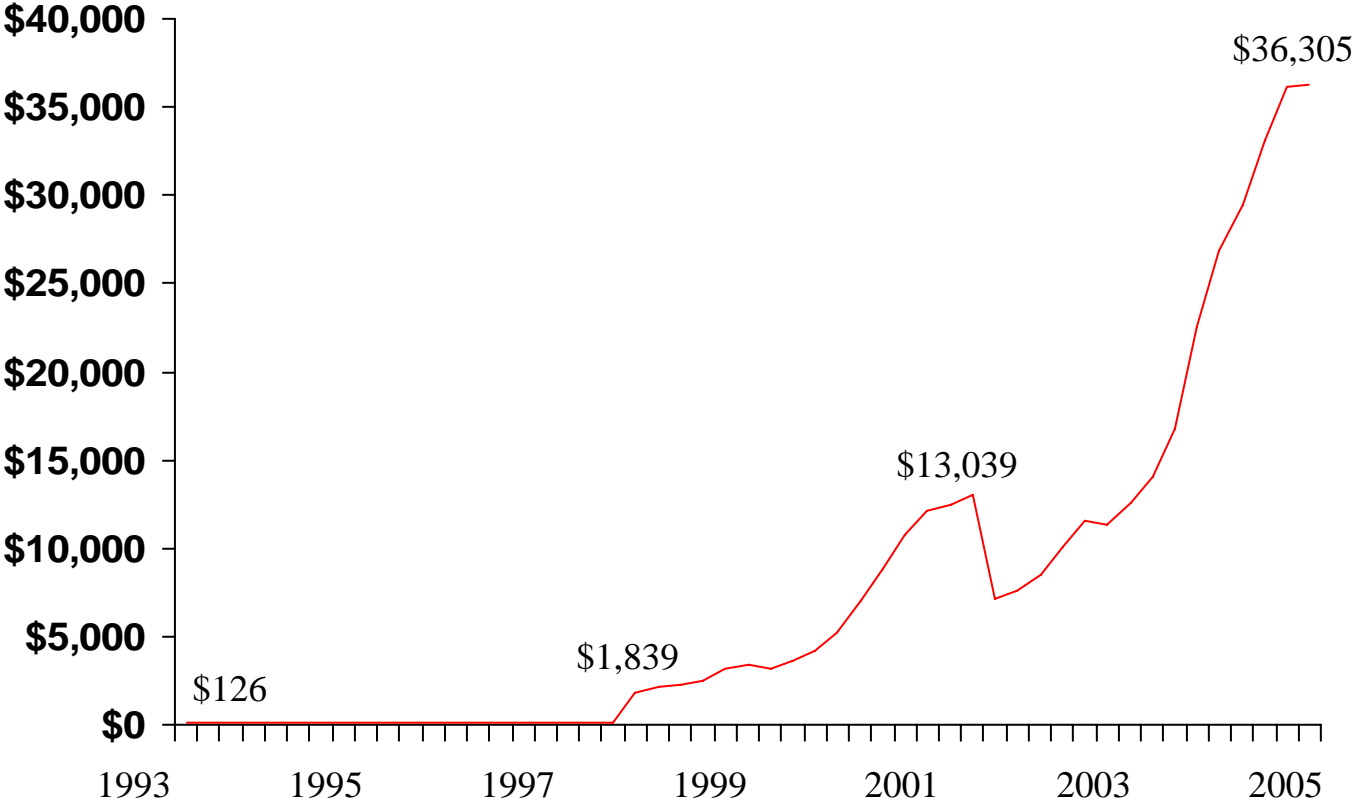
Figure 1: Regimen Market Shares, 1993-2005



Source: IntrinsiQ and SEER.

Note: Market share is measured as the percentage of colon cancer patients who are treated with drugs that are treated with a specific regimen.

Figure 2: Price of Regimens weighted by market shares, 1993-2005



Note: prices are for a 24-week treatment cycle.

Figure 3: Hedonic Price Index and Quality-Adjusted Price Index

