A Quality-Adjusted Price Index for Colorectal Cancer Drugs[*]

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November 2008

PRELIMINARY: PLEASE DO NOT CITE

Abstract

The average price of providing a colorectal cancer patient with a 24-week chemotherapy regimen increased from \$127 in 1993 to \$36,300 in 2005, due largely to the approval and widespread use of five new drugs between 1996 and 2004. We examine whether the substantial increase in spending has been worth it. Using discrete choice methods for demand estimation, we construct a price index for colorectal cancer drugs for each quarter between 1993 and 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 place on drug quality. We find that the naive price index, which makes no adjustments for the changing attributes of drugs on the market, greatly overstates the true price increase. Both the hedonic price index and quality-adjusted price index show that prices have actually remained fairly constant over this 13-year period, with slight increases or decreases depending on the model assumptions.

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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 causing quality-adjusted prices to increase, 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

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[1]Newhouse 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

[2]Cutler (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.

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 of measuring a medical price index. 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 $40 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 chemother-

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apy drug regimen increased from \$127 in 1993 to \$36,300 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 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, neither 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

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[3]13.2 percent of drugs entering Phase 1 trials between 1998 and 2004 were targeting cancer according to the PharmaProjects data base.

[4]Market share data are from IntrinsiQ.

$t - 1$ 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 three additional indices for purposes of comparison. First, we estimate a "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 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. Finally, to assess the implication of the logit assumption we estimate a vertical model in the spirit of Bresnahan (1987).

The naive price index, which increased by 2600 percent between 1993 and 2005, greatly overestimates the price increase. The hedonic price index and the quality-adjusted price indices show that prices have actually decreased slightly over the 13-year period we study. The hedonic and quality-adjusted price indices are similar during the period without innovation, and both exhibit a decrease when the first branded product is introduced in the market. For the following period of innovation the two indices show opposite trends, with the hedonic price

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increasing and the quality-adjusted index decreasing. This discrepancy may be due to the logit functional form assumption, which increases the dimensionality of the problem, and makes all innovation welfare enhancing. In contrast, the vertical model shows an increase in the prices due to innovation of about 28% over the 13-year period. This model is an extreme case, where there are no unobserved shocks to preferences, and the physicians are heterogeneous due to permanent components. The levels of the quality-adjusted logit, vertical 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. For all the models the indices remain fairly constant over the period studied. 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. The probability a patient will survive for five years ranges from 93 percent for those diagnosed with Stage I cancer to eight percent for those diagnosed with Stage IV cancer (NCCN).

Colorectal cancer patients usually begin treatment by having the tumor surgically removed. Most stage 3 and about half of stage 4 patients then receive chemotherapy treatment. For male Medicare patients diagnosed with colorectal cancer between 1998 and 2002, total treatment costs in the first year following diagnosis averaged \$29,600 (Yabroff et al. (2008)). About 70 percent of these costs were due to hospital care, primarily from the initial surgery. In this paper we present an index for chemotherapy drug prices only, not for the total cost of treating the disease. We focus on chemotherapy costs because this is where the innovation has occurred since 1996, and is the likely driver of the increase in treatment costs and improvements in health outcomes.[5] Although chemotherapy costs accounted for about 25 percent of total treatment costs for Medicare colorectal cancer patients in 2001, it may represent the largest cost segment after the average chemotherapy cost per patient increased by \$28,000 between 2001 and 2005.[6]

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.[7]

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[5]Total treatment costs for a Medicare colorectal cancer patient only increased by about \$2,000 in real terms between 1991 and 2001 during a period where most patients were receiving generic chemotherapy drugs.

[6]The 25 percent figure was reported by Joan Warren in a presentation at the International Health Economics meetings in July 2007.

[7]Based on data from IMS Health, 59% of colorectal cancer drugs in the third quarter of 2005 were

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 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 $50,000 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 $1,333 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, fluorororicil, 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 two quality-adjusted price indices. The quality-adjusted

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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.

price indices are constructed from the estimated benefits of innovation that were derived from the estimation of a discrete choice model of demand for colon cancer drugs under two extreme assumptions. 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 the value of these characteristics will overestimate 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 dissaggregation 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

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

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 regiment contains a tablet or not. The time dummies denote quarters and the base quarter is the first quarter of 1993.

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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., worse 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 indices 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 $j \in \{0, \ldots, J_t\}$ at time t are represented by the following indirect utility function

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

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.[8] 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.

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:

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[8]In 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)

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

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. Because price is a function of marginal cost and markups, any exogenous variable that shifts marginal costs or markups should be a valid 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.

One concern with this model is that if physicians earn profits on chemotherapy drugs, profits are correlated with the observed price and/or the attributes, and profits influence physicians prescribing decisions, then the α and β coefficients may be biased. In a 2001 study, the federal government concluded that oncologists could earn profits on most chemotherapy drugs by acquiring them for less than the Medicare reimbursement amount (GAO (2001)). This occurred because

Medicare reimbursed oncologists 95 percent of a drugs listed average wholesale price (AWP), whereas physicians could usually acquire drugs from wholesalers for less than the AWP. For example, physicians were acquiring irinotecan in 2001 for 23 percent less than AWP, on average, which allowed them to earn an approximate 18 percent profit (GAO (2001)).[9]. Most of these profits were eliminated in 2005 when Medicare started reimbursing oncologists based on the actual average selling price (ASP) of a drug rather than the list price (MedPAC (2006)). In the first quarter of 2005, for example, oncologists were acquiring three branded colorectal cancer drugs (bevacizumab, irinotecan, and oxaliplatin) for two or three percent less than the new Medicare reimbursement amount, on average. Jacobson et al. (2006) exploit exogenous variation between oncologists in the generosity of Medicare reimbursement for chemotherapy drugs to estimate the influence of physician profits on treatment decisions. Although they find that oncologists who were reimbursed relatively generously did prescribe more expensive chemotherapy drugs, the magnitude of the effect is small: a one-standard deviation in reimbursement generosity is associated with an increase of about five percent in the cost of chemotherapy prescribed to colorectal cancer patients. Nevertheless, we estimate our models with and without the data from 2005 to see if the results are sensitive to a change in the reimbursement regime. We also present results of an index that uses estimates from the literature for the value of a year of life, or of a quality adjusted life year (QALY), rather than physicians valuations of drug attributes. 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,

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[9]Many oncologists argued that profits on the acquisition of chemotherapy drugs offset Medicares low fees to physicians for administering the drugs

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.

3.3   Vertical Model

Suppose now that the indirect utility of physician/consumer i when he chooses product j in market t is represented by:

$$u_{ijt} = -\alpha_i p_{jt} + \beta x_{jt} + \xi_j + \Delta \xi_j$$

Notice that in this model there is a different α for each consumer i and there is no unobserved shock to preferences. This model is the opposite case of the previous logit model, where all the heterogeneity entered through the error term, while in this model the heterogeneity is present in the random coefficient for price, which is a permanent component. This one-random-coefficient model assumes that consumers agree on the ranking of product quality, and that they only differ

on their willingness to pay for it.[10] In this model there is also an outside option whose utility is normalized to zero. This model, as opposed to the logit one, could potentially predict zero market share for a product.

Ordering products by ascending price, a consumer will buy product j iff $u_{ij} > u_{ik} \forall k \neq j$, which implies

$$\alpha_i < \frac{\delta_j - \delta_k}{p_j - p_k}, \qquad \text{if} \qquad p_j > p_k$$

$$\alpha_i > \frac{\delta_k - \delta_j}{p_k - p_j}, \qquad \text{if} \qquad p_k > p_j$$

Therefore, consumers of type α_i wil buy product j iff

$$\alpha_i < \min_{k<j} \frac{\delta_j - \delta_k}{p_j - p_k} = \overline{\Delta}_j(\delta, p) \qquad \text{and} \qquad \alpha_i > \max_{k>j} \frac{\delta_k - \delta_j}{p_k - p_j} = \underline{\Delta}_j(\delta, p)$$

Assuming $\overline{\Delta}_0(\delta, p) = \infty$ and $\underline{\Delta}_J(\delta, p) = 0$, we can write the market share for product j as:

$$s_j(\delta, p; \Omega, F) = (F(\overline{\Delta}_j(\delta, p)|\theta) - F(\underline{\Delta}_j(\delta, p)|\theta))\mathbb{I}\{\overline{\Delta}_j > \underline{\Delta}_j\} \qquad \text{for} \qquad j = 0, \ldots, J$$

where $\mathbb{I}\{\}$ is an indicator function, Ω are the parameters, and $F(\alpha_i|\theta)$ corresponds to the c.d.f. of α_i, which is assumed to be log-normal.

For all products to have positive market share the following condition has to be satisfied

$$\frac{\delta_J - \delta_{J-1}}{p_J - p_{J-1}} < \cdots < \frac{\delta_2 - \delta_1}{p_2 - p_1} < \frac{\delta_1 - \delta_0}{p_1}$$

and therefore the market shares are computed as

$$s_1(\delta, p; \Omega, F) = F(\frac{\delta_1 - \delta_0}{p_1}|\theta) - F(\frac{\delta_2 - \delta_1}{p_2 - p_1}|\theta)$$

$$s_j(\delta, p; \Omega, F) = F(\frac{\delta_j - \delta_{j-1}}{p_j - p_{j-1}}|\theta) - F(\frac{\delta_{j+1} - \delta_j}{p_{j+1} - p_j}|\theta), \qquad \text{for} \qquad 1 < j < J$$

$$s_J(\delta, p; \Omega, F) = F(\frac{\delta_J - \delta_{J-1}}{p_J - p_{J-1}}|\theta)$$

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[10]Ongoing work extends this model to include more than one random coefficient, and therefore the product ranking is not a matter of consensus across consumers.

The market share of a product is therefore determined by its price-adjusted quality distance from its neighboring products.

The market share equations are inverted recursively to obtain the estimated values of δ as follows:

$$s_{0t} = 1 - F\left(\frac{\delta_{1t} - \delta_{0t}}{p_{1t}}\Big|\theta\right)$$

If p_0 and δ_0 are assumed to be 0, then with data on prices and market share, and the log normal assumption for the distribution of α_i, we can solve for the δ's recursively

$$\delta_{1t} = p_{1t}F^{-1}(1 - s_{0t}|\theta)$$

$$\delta_{jt} = \delta_{j-1,t} + (p_{jt} - p_{j-1,t})F^{-1}(1 - s_{0t} - s_{1t} - \cdots - s_{j-1,t}|\theta)$$

In the estimation stage of this model we estimate all the parameters $\Omega = (\alpha, \beta, \theta)$ by means of a GMM procedure where we exploit the moment conditions of the kind $E(Z'\Delta\xi(\Omega)) = 0$, where Z contains functions of observable attributes uncorrelated with $\Delta\xi(\Omega)$

The price index is computed in a similar way to the previous quality-adjusted price index, with the difference that the unconditional indirect utility is computed by simulating 1000 physicians drawing from the distribution of α_i, and then obtaining $\overline{CV}_t$ as an average of the individuals' compensating variations.

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), which often differs substantially from the true transaction price. We use nominal rather than real prices because any deflator would itself be a price index, and we do not want to build one index on top of another. 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 provides information systems to oncologists to help them determine the proper chemotherapy dosing for their cancer patients. As a result, IntrinsiQ collects monthly data from its oncology clients on the types of chemotherapy drugs used for 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.[11]

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[11]Because 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

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.[12] 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.[13]

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.[14] 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 separately for first- and second-line therapies. Between 1993 and 1996, about 95 percent of colorectal cancer patients were treated with 5-FU/leucovorin, which at that time was generic, with the remainder treated with

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(irinotecan, oxaliplatin, cetuximab, and bevacizumab) actually had colorectal cancer. That is, off-label use accounted for approximately 24 percent of the quantities of these drugs.

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

[13]Data from IntrinsiQ.

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

off-label drugs or regimens with very small market share.[15] 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 (approved as a second-line treatment for metastatic colorectal cancer patients who had already been treated with a different chemotherapy regimen) and irinotecan combined with 5-FU/LV grew at the expense of 5-FU/LV.[16] Capecitabine (Xeloda), a tablet that produces the same chemical response as 5-FU/LV, was approved for treatment of colorectal cancer in April of 2001 and was administered as a standalone therapy or combined with irinotecan. All other drugs for treating colorectal cancer in our sample are delivered intravenously under the supervision of a physician or nurse.

Oxaliplatin (Eloxatin) was introduced in August of 2002, followed by cetuximab (Erbitux) and bevacizumab (Avastin) in February of 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 use market share data from IntrinsiQ rather than SEER. One explanation for these changes is that Medicare patients may be treated with different regimens than non-Medicare patients. Another possible explanation is that the samples used by IntrinsiQ and/or SEER may not be consistent.[17]In order to smooth market shares between the pre- and post-2002 periods, we 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 four quarters of 2002, when the two data sets overlap.

In order to calculate the price per regimen, we require information on the

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[15]5-FU contains the drug fluorororacil.

[16]Because it takes Medicare a while to code new drugs into their proper NDC code, for several quarters a new drug will appear in the outside option.

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

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 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.[18]

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 run by a different firm. 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

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[18]The regimens are priced using data for the contemporaneous quarter only.

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 complete or partial reduction in the size of their tumor (i.e., the response rate); and the mean number of months (across patients in the trial) before their cancer advanced to a more serious state.[19] 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.

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 (second 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

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

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 state. 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 (fifth 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 + oxaliplatin + 5-FU in 2004 increased the median survival time by about four months relative to oxaliplatin + 5-FU/LV, with substantial improvements with one side effect measure and worse performance on the other four measures.

Two new second-line regimens entered the market in 2004 to compete against the first second-line regimen (irinotecan) that was launched in 1996.[20] Cetuximab + irinotecan has a substantially better response rate than irinotecan administered by itself, although median survival is shorter. The new regimen also is superior than irinotecan on all five of the side effect measures.

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

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

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 \$127. The mean price of colorectal cancer drugs increased to \$597 in the first quarter of 1998 when two new irinotecan-based regimens first appeared in the SEER data set.[21] 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 1). 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 848 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 \$8,503 in the third quarter of 2002 to \$12,664 in the third quarter of 2003 (a 49 percent increase), to \$26,811 in the third quarter of 2004 (a 112 percent increase from 2003), and finally to \$36,291 in the third quarter of 2005 (a 35 percent increase from 2004). The prices of the three regimens with the largest market shares 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).

To derive a naive price index that does not account for the changing attributes of the regimens, one would divide the mean prices in Figure 2 by \$127, the mean price in the first quarter of 1993. The shape of the naive index is identical to that of Figure 2, 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. That is, prices increased by

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[21]Irinotecan 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.

28,600 percent between the first quarter of 1993 and the third quarter of 2005.

We next present a price index that does not rely on estimates of how much value physicians place on a drugs efficacy and side effects. In the first four columns of Table 2 we report the year each first-line metastatic regimen was approved, its average price in 2005, the median number of months patients survived when taking the regimen in clinical trials, and a patients expected number of quality adjusted life years (QALYs) based on the performance of the drug in clinical trials. The expected QALY of a drug depends on the amount of time a patient expects to spend in five different health states (i.e., stable metastatic disease with or without side effects; a chemotherapy drug is causing the tumor to shrink with or without side effects; and disease has progressed to a more advanced state) and the utility weight associated with each health state.[22] The utilities weights for each health state, which we average across three studies (Brown and Hutton (1998); Brown et al. (2001); Lloyd et al. (2006)), are 0.68 for stable metastatic disease without a side effect, 0.55 for stable disease with one of six common side effects, 0.82 if the tumor is responding to chemotherapy and the patient is not experiencing a side effect, 0.69 if the tumor is responding but the patient has a side effect, 0.42 if the disease progresses to a more advanced state, and zero for death.[23] In the final three columns of Table 2 we report the incremental cost of each drug relative to 5-FU, the incremental cost per incremental expected life year (relative to 5-FU), and the incremental cost per incremental expected QALY (relative to 5-FU). Most of the drugs have an incremental cost per incremental expected life year between $50,000 and $100,000. The exception, capecitabine, produces the same chemical response as 5-FU but is more convenient because capecitabine can be ingested whereas 5-FU must be infused in a physicians office. Although

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[22]We assume that a patients treatment ceases once the disease advances, so patients no longer experience side effects in that state.

[23]Lloyd et al. (2006) derive utility weights by presenting 100 healthy individuals with a set of standard gambles; Brown and Hutton (1998) and Brown et al. (2001) derive the weights by presenting standard gambles to oncology nurses. A person in perfect health would have a utility weight of one.

there is no consensus among economists, most empirical studies assign a value of $75,000 to $150,000 per life year (Cutler (2004)), and a recent paper placed the value at $373,000 for a 50-year old male (Murphy and Topel (2006)). Most of the drugs have an incremental cost per incremental expected QALY between $100,000 and $150,000. In Figure 3 we plot the mean incremental (relative to 5-FU) cost per incremental (relative to 5-FU) expected life year and expected QALY for patients taking a first-line metastatic regimen other than 5-FU between 1998 and 2005. Specifically, for all first-line regimens other than 5-FU on the market in a particular quarter, we take a weighted average of the cost and expected health outcome, where the weights are the regimen market shares in that quarter. [24] When irinotecan is launched the incremental cost per incremental expected life year is $60,000. This value rises 43 percent by 2002 due to the increasing price of irinotecan and the launch of capecitabine in 2001. The incremental cost then falls with the introduction of oxaliplatin- and bevacizumab-based regimens and is 20 percent higher in the third quarter of 2005 than the first quarter of 1998. By comparison, the consumer price index increased by 19.8 percent during this time period. The mean incremental cost per incremental QALY displays a similar pattern, with a slightly higher peak in 2002. Recall that we use nominal rather than real prices when constructing the indices to avoid building one index on top of another. As a point of reference, however, the consumer price index increased by 35.2 percent between 1993 and 2005. Coefficient estimates from the hedonic regression are reported in Table 3. 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.[25]

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

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[24]Because we omit 5-FU and the second-line regimens, the weights sum to one in each quarter.

[25]We did not include other second-line attribute interactions due to multi-colinearity.

a 64.2 percent increase in the price of a regimen.[26] 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 before the products are approved and marketed. It is quite plausible, therefore, that at any given point in time there could 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.

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[26] $0.642 = \exp(0.496) - 1$.

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 4. The pattern of prices for the hedonic index (the lower line) in Figure 4 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 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 0.71 to 0.85. The price index jumped by six points with the introduction of the oxaliplatin-based regimens in 2002, and has remained fairly constant since then during the time when cetuximab and bevacizumab were launched.

In the same figure we show the quality-adjusted price index. The quality-adjusted index is very similar to the hedonic price index during the period where

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only 5-FU/LV was present. There is a decrease of 28 points during 1998, when irinotecan started showing positive market shares.[27] That decrease after the introduction of irinotecan was also present in the hedonic price index in 1996. During the period 1999 to 2001, the quality-adjusted price index slowly increases as does the hedonic price index, but in 2002 when oxaliplatin is introduced their predictions differ. 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. The 8-percentage point decrease in the quality-adjusted price index after the introduction of oxaliplatin contrasts with the 6 percentage points increase in the hedonic price index. Finally, the quality-adjusted price index remains decreasing towards the end of our period of analysis. Contrasting with the previous two models, the vertical model shows that innovation results in moderate, but positive price increases. The parameter estimates for this model and the distribution of the price coefficient are shown in Table 4 and Figure 4 respectively, and the distribution of the random coefficient on price is presented in Figure 5

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 two quality-adjusted price indices. The conclusions about the evolution of prices of new pharmaceutical developments differs substantially between the naive price index and the three methods that take into account changing product attributes. While the naive price index shows

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

a dramatic increase in prices over the 13-year period we study, the hedonic price and the quality-adjusted price index show slight decreases, and slight increase in the case of the vertical model. 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.[28] Ongoing research will refine these estimates using frontier discrete choice methods for demand estimation.

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[28]Pharmaceutical and biotech firms may in turn transfer some of the welfare gains to physicians by offering rebates when they purchase a sufficiently large quantity of a companys chemotherapy drugs.

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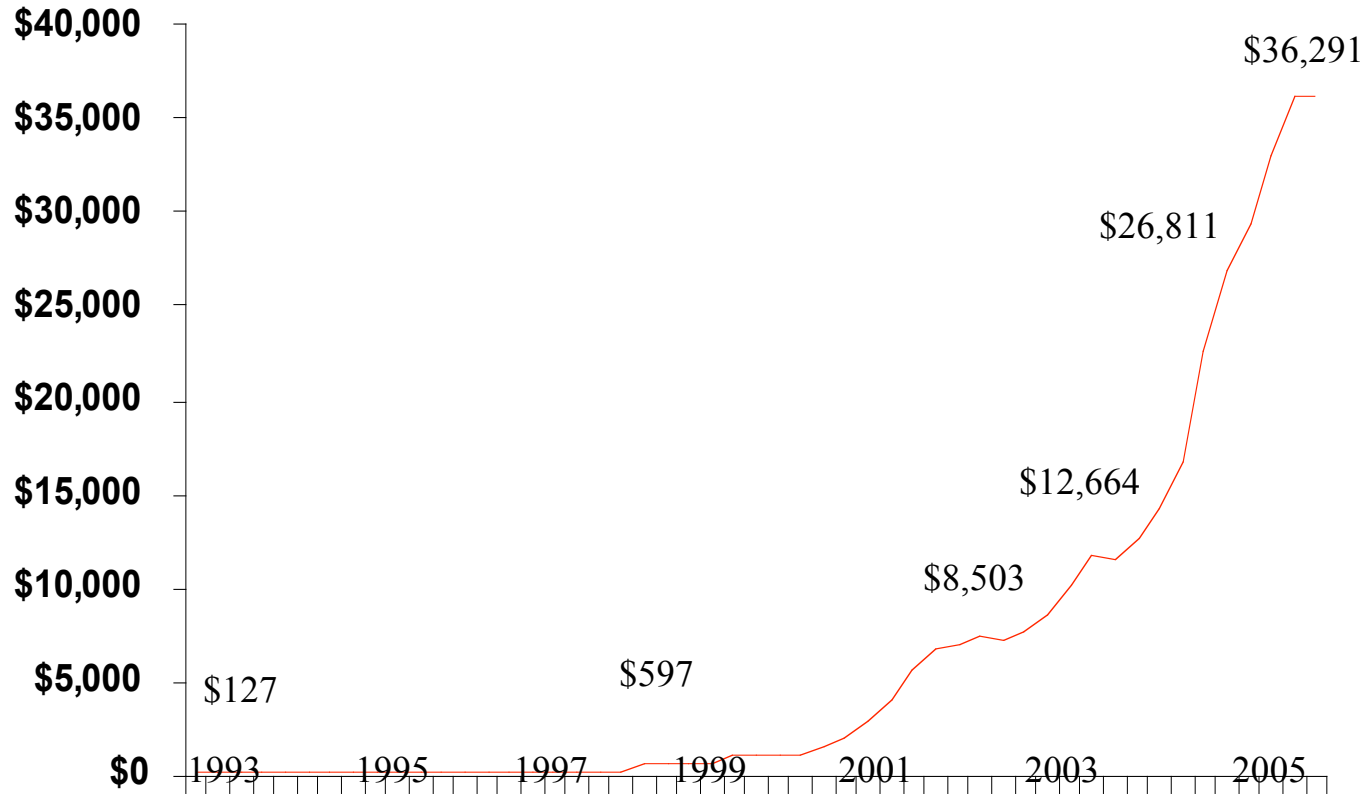
Figure 1: Regimen Market Shares, 1993-2005
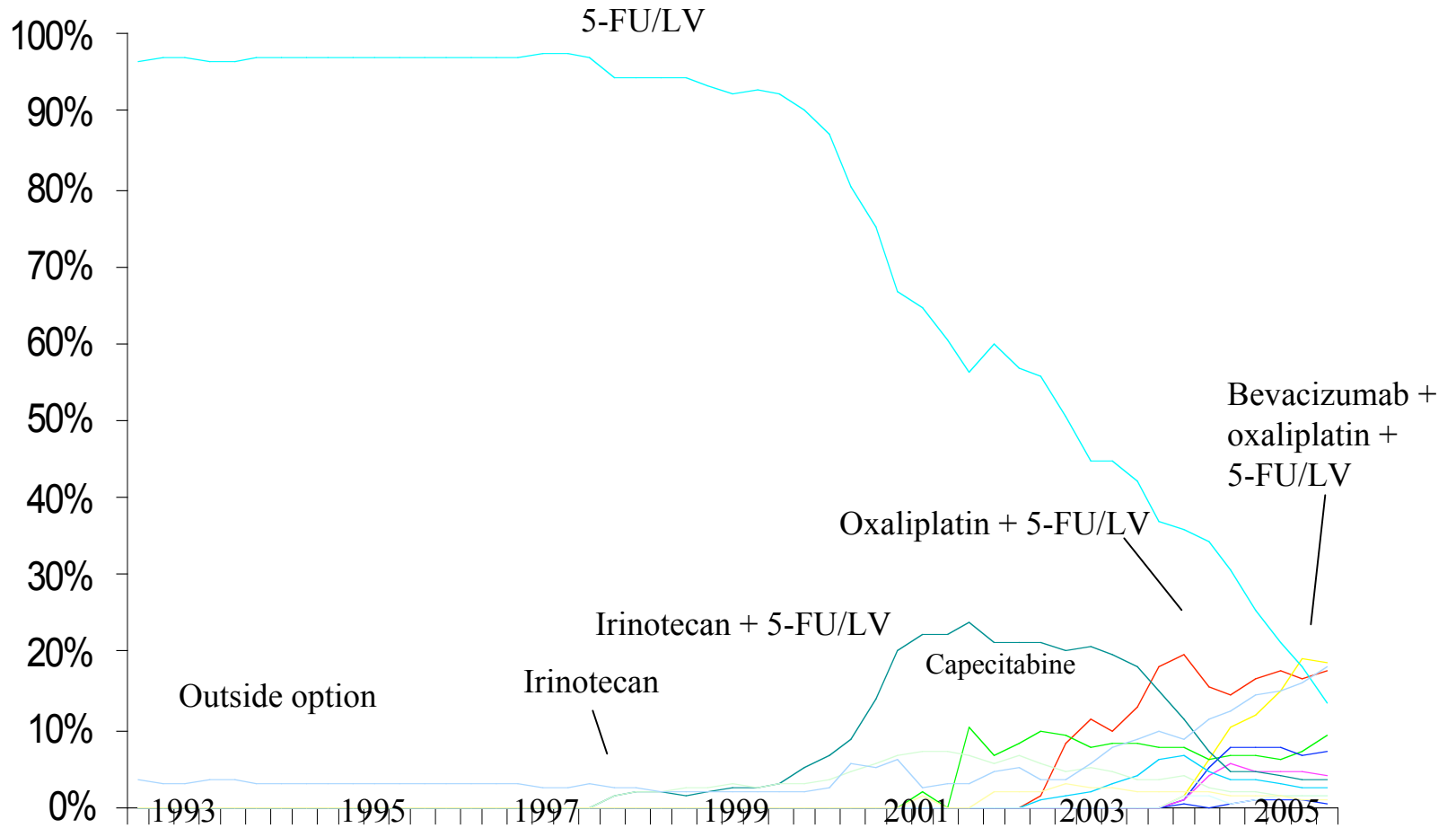
Source: IntrinsiQ and SEER.
Market share is measured as the percentage of colon cancer patients who are treated with drugs that are treated with a specific regimen.

Figure 2: Price of Regimens Weighted by Market Shares, 1993-2005

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

Figure 3: Incremental Cost of First-Line Metastatic Regimens Per Incremental Expected Health Outcome, Relative to 5-FU, 1998 - 2005
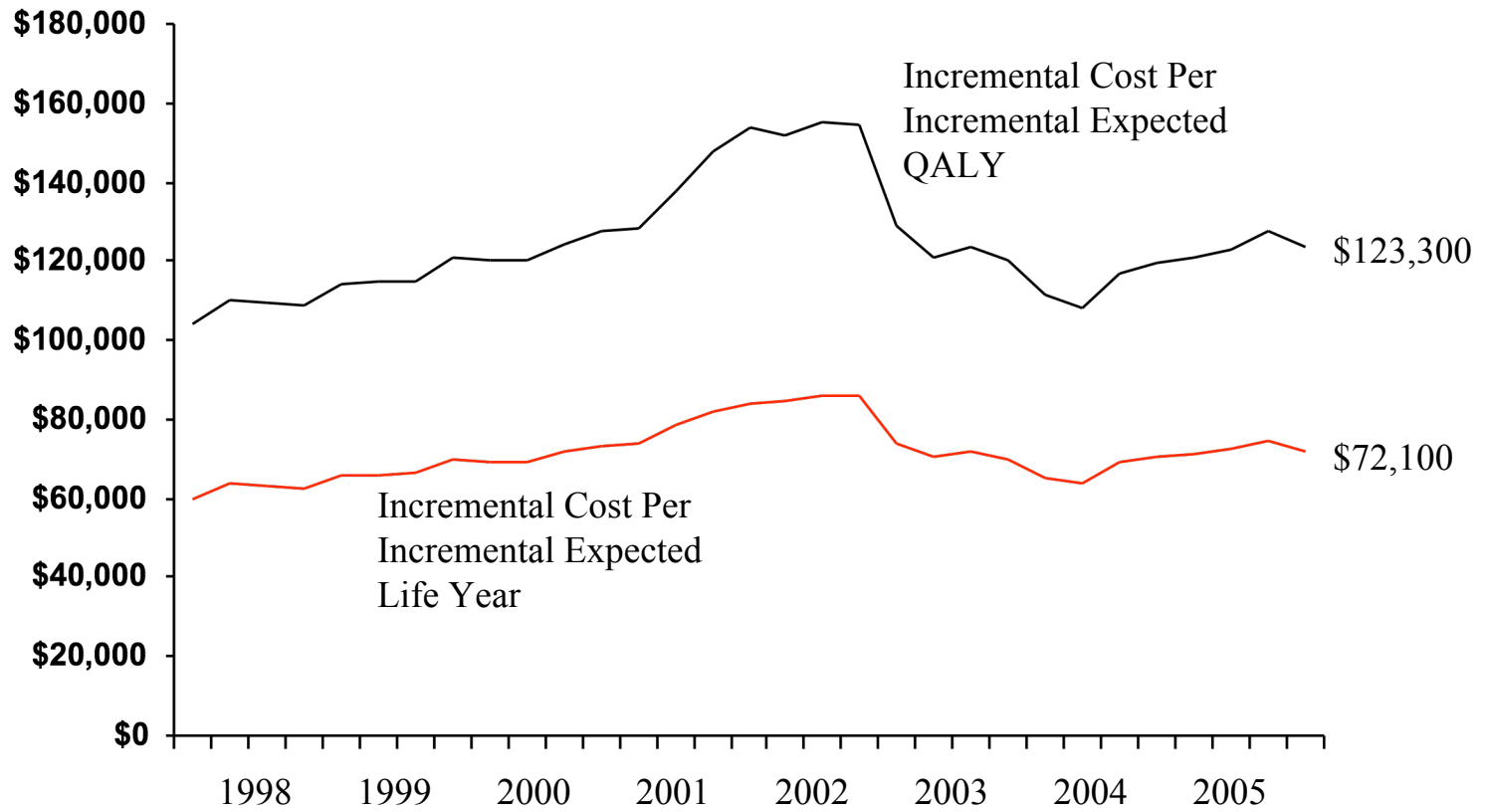
Note: cost and health outcomes are relative to 5-FU.

Figure 4: Hedonic and Quality-Adjusted Price Indices

Legend: hedonic, quality-adj logit, quality-adj vertical

Table 1: Attributes of the Drug Regimens

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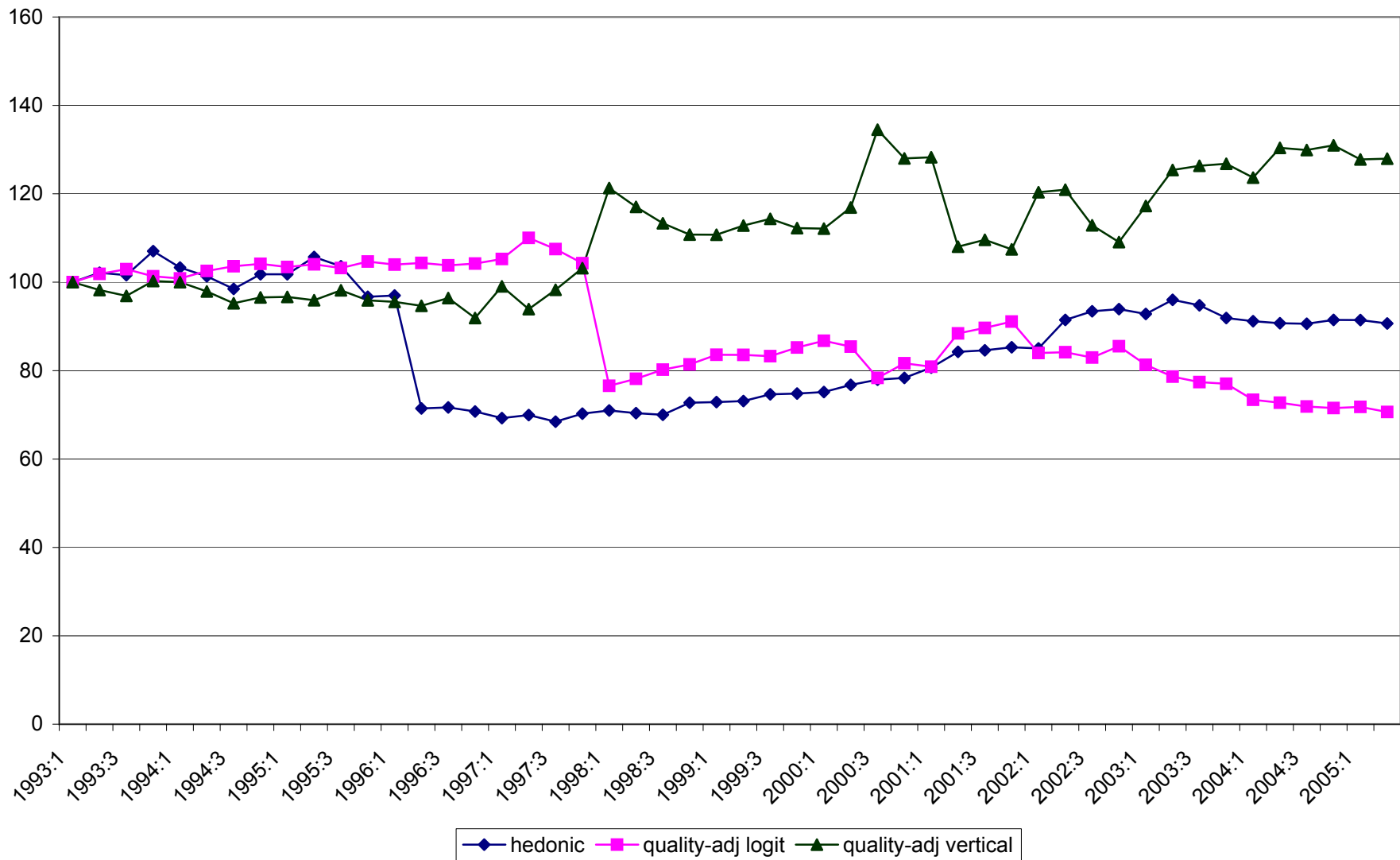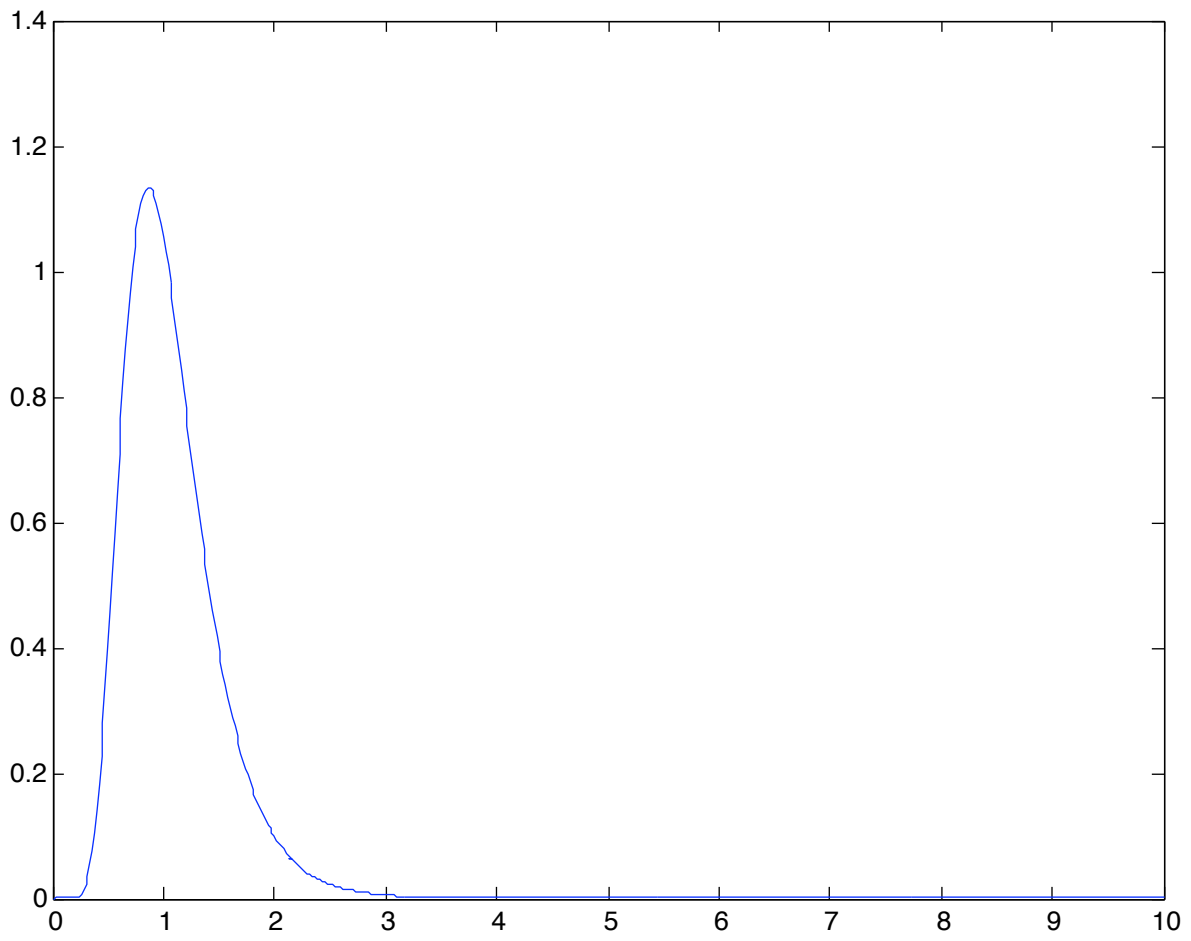|		**Efficacy Measures**			**Grade 3 or Grade 4 Side Effects (%)**				
Regimen	Launch Year	Survival Months	Response Rate	Time to Progression	Abdominal Pain	Diarrhea	Nausea	Vomi-ting	Neutro-penia
First-line therapies									
5-FU + Leucovorin	1991	12.5	20.8	4.7	5.5	10.4	4.8	4.4	33.7
Irinotecan (Camptosar) + 5-FU/LV	1996	15.6	35.4	6.7	5.3	24.0	11.9	8.0	39.5
Capecitabine (Xeloda)	2001	13.1	21.0	4.4	9.5	15.0	4.0	4.5	3.0
Irinotecan + capecitabine	2001	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 (Avastin) + oxaliplatin + 5-FU/LV	2004	23.2	41.0	9.9	8.0	23.1	7.9	8.6	12.2
Bevacizumab + oxaliplatin + capecitabine	2004	23.2	41.0	9.9	8.0	23.1	7.9	19.0	12.0
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									
Irinotecan	1996	9.5	15.0	4.2	16.0	31.0	17.0	12.0	26.0
Cetuximab (Erbitux)	2004	N/A	10.8	1.5	14.0	2.0	2.0	6.0	5.0
Cetuximab + irinotecan	2004	6.1	22.9	4.1	8.0	22.0	6.0	7.0	5.0

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 Phase clinical 3 trials. The median survival is measured in months. One cetuximab regimen 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. Time to progression is the mean number of months for a tumor to advance to a more severe stage. 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 experienced 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

Cost and Expected Health Outcomes of First-Line Metastatic Chemotherapy Regimens

1st Line Metastatic Regimens	Year Approved in U.S.	Average Cost, 2005	Expected Survival (Months)	Expected QALYs (Months)	Incremental Cost	Incremental Cost Per	
						Incremental Expected Life year	Incremental Expected QALY
Fluorouracil + leucovorin (5-FU)	1991	$75	12.5	0.53	------	------	------
Irinotecan + 5-FU	1996	$21,386	15.6	0.68	$21,311	$82,494	$142,988
Capecitabine	2001	$9,224	13.1	0.54	$9,149	$182,980	$974,276
Irinotecan + capecitabine	2001	$20,124	15.6	0.68	$20,049	$77,609	$134,521
Oxaliplatin + 5-FU	2002	$25,426	19.4	0.88	$25,351	$44,089	$72,117
Oxaliplatin + capecitabine	2002	$31,936	18.0	0.80	$31,861	$69,515	$116,755
Bevacizumab + oxaliplatin + 5-FU	2004	$76,636	23.2	1.04	$76,561	$85,863	$148,251
Bevacizumab + oxaliplatin + capecitabine	2004	$57,541	23.2	1.04	$57,466	$64,448	$111,276
Bevacizumab + irinotecan + 5-FU	2004	$46,991	20.3	0.94	$46,916	$72,178	$113,411

Table 2

Coefficient Estimates from Hedonic Regression

	Coefficient	Standard Error
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

	Coefficient	Standard Error
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.

Table 4

	Coefficient	Standard Error
$\log(\alpha) \sim N(0,\theta)$	0.378	
Efficacy measures:		
General survival (months)	0.203	
Response rate (percentage)	0.376	
Response rate * second line therapy	0.055	
Time to progression (months)	-1.579	
Grade 3 or 4 side effects:		
Diarrhea	0.147	
Nausea	-0.192	
Abdominal pain	0.203	
Neutropenia	-0.044	
Tablet	0.156	
Constant	5.072	
Observations	208	
GMM obj.	2.1499×10^{-21}	

Notes: The regressions include a full set of quarter indicator variables.

Appendix: Composition and Dosages of the Chemotherapy Regimen

Regimen	1st Drug	2nd Drug	3rd Drug	4th 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	200 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			

[20] Mayo treatment method.
[21] FOLFIRI treatment method.
[22] FOLFOX treatment method.

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		
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	200 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; m^2 = 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 m^2 and weighs 80 kilograms.

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

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[23] CAPOX treatment method.