Pricing in the Market for Anticancer Drugs[†]

David H. Howard, Peter B. Bach, Ernst R. Berndt, and Rena M. Conti

I n 2004, Genentech introduced the drug bevacizumab—brand name Avastin— for patients with late-stage colorectal cancer. The drug cost $50,000 per treatment episode and was associated with an incremental increase in life expectancy of five months. Following Genentech's pricing announcement, newspapers ran stories with titles like "Cancer Weapons, Out of Reach" in the *Washington Post* (Wittes 2004) and "Price of Cancer Drugs Called 'Mind-Boggling'" in *USA Today* (Szabo 2004). Some Wall Street analysts worried that bevacizumab's pricing would prompt the US Congress to regulate drug prices (Anand 2007). By 2011, the backlash against bevacizumab was a distant memory. Bristol-Myers Squibb set the price of its newly approved melanoma drug ipilimumab—brand name Yervoy—at $120,000 for a course of therapy. The drug was associated with an incremental increase in life expectancy of four months.

■ *David H. Howard is Associate Professor, Department of Health Policy and Management, Rollins School of Public Health, and Department of Economics, Emory University, Atlanta, Georgia. Peter B. Bach is a Member in the Department of Epidemiology and Biostatistics, Attending Physician in the Department of Medicine, and Director of the Center for Health Policy and Outcomes, Memorial Sloan Kettering Cancer Center, New York City, New York. Ernst R. Berndt is the Louis E. Seley Professor in Applied Economics, Sloan School of Management, Massachusetts Institute of Technology, Cambridge, Massachusetts. Rena M. Conti is Assistant Professor of Health Policy, Departments of Pediatrics and Public Health Sciences, University of Chicago, Chicago, Illinois. Their email addresses are david.howard@emory.edu, bachp@mskcc.org, eberndt@mit.edu, and rconti@uchicago.edu.*

Drugs like bevacizumab and ipilimumab have fueled the perception that the launch prices of new anticancer drugs and other drugs in the so-called "specialty" pharmaceutical market have been increasing over time and that increases are unrelated to the magnitude of the expected health benefits (Experts in Chronic Myeloid Leukemia 2013; Kantarjian, Fojo, Mathisen, and Zwelling 2013; Schrag 2004; Hall 2013). A commentary in *The Lancet*, a leading British medical journal, summarized the conventional wisdom: "[T]he cost of the new generation of drugs is getting out of all proportion to the added benefit" (Cavalli 2013). The public debate has focused on a handful of high-profile drugs like bevacizumab. It is unclear in these debates whether these drugs are outliers or reflect broader trends in the industry.

In this paper, we discuss the unique features of the market for anticancer drugs and assess trends in the launch prices for 58 anticancer drugs approved between 1995 and 2013 in the United States. Drugs used to treat other conditions have also been closely scrutinized—most recently the $84,000 hepatitis C treatment Sovaldi—but we restrict attention to anticancer drugs because the use of median survival time as a primary outcome measure provides a common, objective scale for quantifying the incremental benefit of new products.

The market for anticancer drugs is economically significant. Within the market for pharmaceuticals, anticancer drugs rank first in terms of global spending by therapeutic class: $91 billion in 2013, up from $71 billion in 2008 (IMS 2014). The US market size was $37 billion in 2013, of which one-third was spent on 10 patent-protected cancer drugs alone (Conti, Bernstein, Villaflor, Schilsky, Rosenthal, and Bach 2013). The market is also politically salient. Anticancer drugs figure prominently in discussions over health reform, alternately symbolizing wasteful spending and biomedical progress.

We find that the average launch price of anticancer drugs, adjusted for inflation and health benefits, increased by 10 percent annually—or an average of $8,500 per year—from 1995 to 2013. We review the institutional features of the market for anticancer drugs, including generous third-party coverage that insulates patients from drug prices, the presence of strong financial incentives for physicians and hospitals to use novel products, and the lack of therapeutic substitutes. We argue that under these conditions, manufacturers are able to set the prices of new products at or slightly above the prices of existing therapies, giving rise to an upward trend in launch prices. Government-mandated price discounts for certain classes of buyers may have also contributed to launch price increases as firms sought to offset the growth in the discount segment by setting higher prices for the remainder of the market.

Drug Pricing Strategies

The process by which firms establish the "launch prices" of new, branded drugs—that is, the prices firms set immediately following US Food and Drug Administration (FDA) approval—is opaque, and relatively little work has been done on the

subject.[1] At the time of FDA approval, most drugs are on-patent, and so manufacturers are temporary monopolists. They have wide leeway, though not unlimited power, to set prices.

Reekie (1978) and Lu and Comanor (1998) studied the determinants of drugs' launch prices for drugs across multiple therapeutic categories. They found that prices are higher for drugs that offer significant benefits compared to existing products. Hedonic pricing studies of colorectal cancer (Lucarelli and Nicholson 2009) and anti-ulcer drugs (Suslow 1996; Berndt, Bui, Reiley, and Urban 1995) find that manufacturers set higher prices for higher-quality drugs, but studies of antidepressants (Chen and Rizzo 2012) and arthritis drugs (Cockburn and Anis 2001) actually find the opposite. In most therapeutic categories physicians and patients learn about drug quality partly through experience, and so manufacturers may find it advantageous to introduce high-quality drugs at low prices so that the drugs will penetrate the market more quickly (Chen and Rizzo 2012).

Anticancer Drugs

Anticancer drugs are among the only life-prolonging treatments available for patients with metastatic tumors, which means that the tumor has spread beyond its original site to a nonadjacent location. The vast majority of patients with metastatic disease will die of cancer. It has become increasingly common to administer anticancer drugs to patients with early-stage disease after they have undergone surgery or radiotherapy. Because most newly approved anticancer drugs are approved on the basis of their effectiveness in patients with metastatic disease, our analysis focuses on this group of patients.

Rapid progress in the fields of tumor biology, genetics, and immunology has spurred the development of a number of new anticancer drugs. Almost 1,000 anticancer drugs are currently in various phases of pre-approval testing, more than the number for heart disease, stroke, and mental illness combined (IMS 2014; PhRMA 2014). Many new drugs are approved for the treatment of tumors with particular genetic markers. For example, the FDA approved pertuzumab in 2012 for patients with metastatic breast cancer linked to a defective HER2 gene. Targeted therapies are more likely to succeed in clinical trials and may face a less-elastic demand curve, facilitating premium pricing (Trusheim and Berndt 2012).

The scientific knowledge embodied by new drugs is impressive, but progress in basic science has not always been accompanied by proportionate improvements in patient outcomes. Gains in survival time associated with recently approved anticancer drugs are typically measured in months, not years.

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[1] Prior work on pricing in the pharmaceutical industry has mostly focused on the effect of generic competition on price levels (for example, Caves, Whinston, and Hurwitz 1991) and post-entry pricing dynamics (Lu and Comanor 1998).

Most anticancer drugs are approved by the FDA on the basis of one or more randomized controlled trials. Some trials have an "active control"; patients are randomized to receive the new drug or an alternative therapy. When a drug is sufficiently novel that it has no close substitutes or it will be used in combination with existing drugs, patients in the control arm may be randomized to receive the new drug or a placebo. Trials of anticancer drugs usually measure patient outcomes in terms of the difference in survival between the treatment and control arms.

Some drugs are approved on the basis of single-arm trials. In a single-arm trial, all patients receive the new drug. There is no control group. Single-arm trials focus on short-term patient safety rather than patient survival, and so they have a much shorter duration. The FDA grants approval for many leukemia and lymphoma drugs on the basis of single-arm trials. Median survival among patients with these types of cancers is two or more years. Requiring manufacturers of leukemia and lymphoma drugs to conduct randomized trials to measure survival benefits could significantly delay the introduction of potentially beneficial drugs. Single-arm trials can show that a drug is safe but cannot determine whether the drug improves life expectancy. Physicians can observe survival in their own patient populations, but it is probably difficult for individual physicians to draw sound inferences about the quality of a new drug because their patient panels are not sufficiently large. Unlike single-arm studies, randomized trials establish efficacy as common knowledge.

Economists have measured the value of anticancer drugs by evaluating changes in life expectancy and costs over time (Howard, Kauh, and Lipscomb 2010; Lichtenberg 2009a, b; Sun, Jenna, Lakdawalla, Reyes, Philipson, and Goldman 2010; Woodward, Brown, Steward, Cronin, and Cutler 2007) or measuring patients' willingness-to-pay (Goldman, Jena, Lakdawalla, Malin, Malkin, and Sun 2010; Lakdawalla, Romley, Sanchez, Maclean, Penrod, and Philipson 2012; Romley, Sanchez, Penrod, and Goldman 2012; Seabury, Goldman, Maclean, Penrod, and Lakdawalla 2012; Snider, Romley, Vogt, and Philipson 2012). A common finding is that the dollar-denominated benefits associated with anticancer drugs are equal to or exceed the cost of an episode of treatment. However, willingness-to-pay estimates must be interpreted cautiously in light of the fact that most patients mistakenly believe that anticancer drugs cure cancer (Weeks et al. 2012). In addition, these past studies do not address trends in launch prices. If new drugs have higher prices per unit of benefit, then we cannot assess the cost-effectiveness of anticancer drugs as a class based on studies of older drugs.

Policies Governing Drug Coverage and Reimbursement

Medicare is the most prominent US payer for anticancer drugs, followed by commercial insurers and then state Medicaid programs. Medicare pays for physician-administered intravenous drugs through the medical "Part B" benefit. By law, Medicare does not directly negotiate with drug manufacturers over prices for prescription drugs covered under the Part B benefit or the oral anticancer drugs

covered under Medicare's pharmacy "Part D" benefit. Section 1861 of the Social Security Act, which requires that the Medicare program cover "reasonable and necessary" medical services, precludes consideration of cost or cost-effectiveness in coverage decisions (Neumann 2005). Consequently, Medicare covers all newly approved anticancer drugs for indications approved by the FDA.

The private insurance plans that provide prescription drug coverage under Medicare "Part D" are required to cover all drugs in six protected classes, one of which is anticancer drugs (Center for Medicare and Medicaid Services 2014). Three quarters of the population reside in states that require insurers to cover anticancer drugs for "off label," non-FDA-approved uses (Bach 2009).

Insurers in states without these requirements and large employers that self-insure have more leeway to determine coverage policies, yet, in the rare instances where third-party payers have tried to place meaningful restrictions on patients' access to anticancer drugs, they have relented under pressure from clinicians and patient advocacy groups. In the early 1990s, many insurers refused to cover a breast cancer treatment consisting of higher-than-normal doses of anticancer drugs followed by a bone marrow transplant. Breast cancer patient advocacy groups waged a high-profile campaign to secure coverage, and most insurers started paying for the treatment. Randomized trials later found that it did not prolong survival, and physicians and patients abandoned the procedure (Howard et al. 2011).

Oregon's Medicaid program recently proposed to limit coverage of anticancer drugs on the grounds that "in no instance can it be justified to spend $100,000 in public resources to increase an individual's expected survival by three months when hundreds of thousands of Oregonians are without any form of health insurance" (as reported in Landsem 2013). The proposal was withdrawn following a public backlash.

The case of bevacizumab illustrates the laxity of payers' coverage policies. The FDA approved the drug for the treatment of colorectal cancer in 2004 and then for treatment of breast cancer in 2008 based on the results of a randomized trial. Results from two additional randomized trials were later released in 2009. The trials found that patients receiving bevacizumab experienced a statistically significant gain in "progression-free survival," which measures the period of time where the cancer is under control, but that differences in overall survival were small and not statistically significant. Based on these findings, the FDA revoked coverage for bevacizumab's breast cancer indication in 2011. However, an expert panel convened by the National Comprehensive Cancer Network (2010), a consortium of major cancer centers, voted against removing bevacizumab from its list of appropriate breast cancer drugs. Faced with these conflicting decisions, Medicare and major multistate insurance plans announced they would continue to cover bevacizumab for breast cancer patients.

Some drug industry critics hold up the British National Health Service as a model for restraining drug prices. Britain's National Institute for Clinical Effectiveness evaluates the cost-effectiveness of new drugs and has restricted National Health Service funding for cancer drugs where the benefits are small in relation to costs. The British government uses the threat of noncoverage to negotiate discounts with drug

manufacturers. However, restrictions on patient access are unpopular, and Prime Minister David Cameron created a 200 million pound Cancer Drugs Fund in 2011 to pay for noncovered cancer drugs outside of normal funding channels (Fleck 2013).

The oncologists who provide care to cancer patients face financial incentives to administer intravenous anticancer drugs. In most industries, there is not much difference between wholesale and retail prices, and so these prices send consistent signals. But wholesale and retail prices for drugs can diverge systematically, providing incentives for dysfunctional behavior. Oncologists and hospitals buy intravenous, physician-administered drugs from wholesalers and bill insurers. They profit on the spread between the reimbursed price and the wholesale cost. Medical oncology practices derive more than 50 percent of their revenues from drugs (Akscin, Barr, and Towle 2007), and many oncologists report that they face financial incentives to administer anticancer drugs (Malin, Weeks, Potosky, Hornbrook, and Keating 2013). Oncologists' drug choices are responsive to profit margins (Conti, Rosenthal, Polite, Bach, and Shih 2012; Jacobson, O'Malley, Earle, Pakes, Gaccione, and Newhouse 2006; Jackobson, Earle, Price, and Newhouse 2010). The use of irinotecan—brand name Camptosar—decreased following the expiration of its patent, even though the price dropped by more than 80 percent, possibly reflecting declines in the spread between the reimbursement level and oncologists' acquisition cost (Conti et al. 2012).

Insurers use cost-sharing—that is, copayments, coinsurance, and deductibles—to make patient demand responsive to the cost of health care, but cost sharing is not always effective in reducing patients' demand for anticancer drugs. Most employer-based insurance policies have an annual out-of-pocket maximum, beyond which the insurer assumes 100 percent of the cost of care. Many patients with late-stage cancer reach the maximum fairly quickly, in which case the insurer bears the full cost of anticancer drugs for the remainder of the benefit year.[2] Consequently, patients may be indifferent between a drug that costs $20,000 and one that costs $100,000.

An analysis of private insurance claims data from 1997 to 2005 found that the annual median out-of-pocket cost for the intravenous drug rituximab was $431 per year (Goldman et al. 2010). Patients' costs were less than 2 percent of total spending on rituximab. Patients' out-of-pocket costs for oral agents, which are covered under insurers' pharmacy benefit, are higher. Still, a separate analysis of claims found that cancer patients' out-of-pocket costs were 5 percent of total drug costs, and only 34 percent of patients faced per claim copayments in excess of $50 (Raborn, Pelletier, Smith, and Reyes 2012).

Even when patients face large out-of-pocket costs for anticancer drugs, they have several options for reducing their liabilities. Patients with private insurance can apply for aid from drug manufacturers' co-pay assistance programs, which offset patients' out of-pocket costs, typically on generous terms. For example, Dendreon's

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[2] In the past, some plans did not count spending on prescription drugs towards the out-of-pocket maximum, but this practice is prohibited by the Patient Protection and Affordable Care Act of 2010, beginning in 2014.

patient assistance program covers up to $6,000 of patients' copayments, coinsurance, and deductibles for its $93,000 prostate therapy sipuleucel-T, boasting "75 percent of patients receiving Provenge [the trade name for sipuleucel-T] are expected to have minimal to no out-of-pocket costs" (Dendreon 2014). The program even reimburses patients for the costs they incur during travel to oncology clinics. These funds flow directly from pharmaceutical companies to patients and are not captured in insurers' records. Patient assistance programs lower the elasticity of patient demand, enabling manufacturers to set higher prices (Howard 2014). The federal government does not allow assistance programs affiliated with a pharmaceutical manufacturer to aid Medicare and Medicaid enrollees on the grounds that these programs provide an illegal inducement for patients to receive care, but manufacturers are allowed to donate funds and steer Medicare and Medicaid patients to programs operated by independent foundations. Patients can also use death as a backstop against medical debt. Most patients considering whether to use anticancer drugs have short life expectancies. They may be willing to exhaust their assets to buy small gains in health. Health care providers must write-off debt in excess of the decedent's estate.

Not surprisingly, the elasticity of demand with respect to patients' out-of-pocket costs is low. Goldman et al. (2006) estimate that spending on cancer drugs declines by 0.1 percent in response to a 10 percent increase in patient coinsurance. For the sake of comparison, spending on drugs used to treat arthritis declines by 2.1 percent and spending on drugs used to treat kidney failure declines by 0.7 percent when patient coinsurance increases by 10 percent.

Trends in Launch Prices

We evaluate pricing trends for 58 anticancer drugs approved in the US between 1995 and 2013 (CenterWatch 2014). We restrict attention to drugs administered with the primary intent of extending survival time for cancer patients and drugs for which survival benefits have been estimated in trials or modeling studies. We do not consider drugs administered to treat pain or drugs that are administered to alleviate the side effects of cancer treatments. Details about the selection of drugs, references for survival benefits, and other details about the data are provided in an Appendix available with this paper at the journal's website, http://e-jep.org.

The FDA approves drugs for specific uses, or indications, which are described in each drug's "product label." We focus on the benefits associated with each drug's first FDA-approved indication. Once a drug is FDA-approved, physicians are free to use the drug for any patient with any condition, but manufacturers may not promote the drug for "off label" indications. We did not consider the survival benefits associated with indications approved by the FDA after the initial approval of the drug. In most cases, the benefits associated with these indications are unknown to manufacturers at the time of launch and are thus difficult to incorporate into their initial pricing decisions.

Forty-one of the 58 drugs in our sample were approved on the basis of randomized controlled trials. We obtained information on the incremental survival benefits of these drugs from the results of these trials. Drugs are typically tested against the next-best therapy available at the time the trial was initiated. In some cases the next-best therapy is "nothing," and so patients receive a placebo. We measured benefits by subtracting median overall survival in the control arm from median overall survival in the treatment arm. We used progression-free survival (the period of time the cancer is under control) when trials did not report overall survival.[3] Drug manufacturers may focus on progression-free survival for practical reasons. Trials designed to detect differences in progression-free survival are shorter (progression precedes death) and require a smaller sample size because the variation in progression-free survival is typically lower than the variation in overall survival. There is considerable debate in the oncology community about whether progression-free survival is a good proxy for overall survival. Our view is that even if progression-free survival benefits are only weakly correlated with overall survival benefits, data on progression-free survival benefits provide a useful signal of product quality to a manufacturer who must set a price for a new drug in the absence of information on overall survival benefits and to practicing physicians who must decide whether to use it. In our data, we observe both overall survival and progression-free survival for 20 drugs. The absolute difference between overall survival and progression-free survival is less than one month for five of these drugs and less than two months for 13 of the drugs.

For the 17 drugs that were approved on the basis of single-arm trials, we obtained estimates of survival benefits from post-approval trials ($N = 6$) and cost-effectiveness studies that use simulation models to project survival ($N = 11$). Cost-effectiveness studies typically report benefits in terms of mean life expectancy or mean quality-adjusted life-years. We converted these quantities to median survival gains assuming survival time is distributed exponentially.[4]

We calculated the "episode treatment price" for each drug, which equals each drug's monthly cost to the Medicare program in 2013 dollars (see Bach 2009 for details) multiplied by the typical duration of treatment in months. Medicare costs represent the actual dollar amounts Medicare, the largest public insurance program, pays for drugs. In most cases, Medicare reimbursements will be greater than the prices hospitals, physicians, and pharmacies pay to wholesalers. We do not believe that rebates—refunds from manufacturers to hospitals, physicians, pharmacies, and third party insurers—are large in the market for new anticancer drugs, but pricing is opaque and rebate arrangements are closely guarded. Medicare has adjusted its payment formulae over time to align reimbursement and wholesale prices more closely. For this reason, our price series may understate increases in providers' acquisition prices. As we describe below, drug acquisition costs vary

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[3] Trials report medians, because measurement of means is possible only after all patients in the trial are dead. Some trials are not powered to detect changes in overall survival but report it anyway.

[4] If we assume survival time is distributed exponentially, it is possible to convert means to medians without estimating ancillary shape parameters. Median survival is equal to mean survival multiplied by $\ln(2)$.

Figure 1
**Drug Prices versus Life Years Gained**
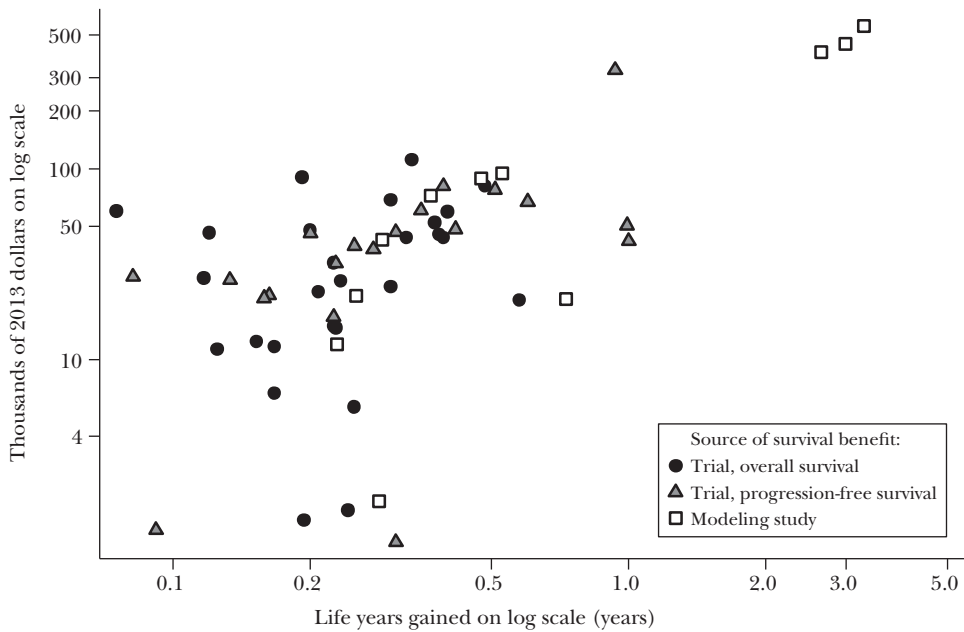
Source: Authors.

between providers and pharmacies, and Medicare payment rates do not account for differences in acquisition costs across various categories of buyers.

Our approach accounts for differences in the duration of treatment across drugs and is consistent with the notion of measuring the price of a treatment episode, as advocated by Berndt, Cutler, Frank, Griliches, Newhouse, and Triplett (2000) and Busch, Berndt, and Frank (2001). However, a drug's treatment episode price is not a comprehensive measure of the impact of that drug on health care costs. The impact of a drug on total costs depends on whether it is a substitute or complement to existing treatments and whether it increases or decreases the incidence of side effects, some of which can be quite costly to treat.

Prices versus Survival Benefits over Time

Figure 1 plots treatment-episode prices in 2013 dollars against incremental survival benefits, both on the natural log scale. The average drug price is $65,900 (in 2013 dollars), and the average survival benefit is 0.46 years. The markers identify drugs based on the source of survival benefit data: overall survival from a randomized trial; progression-free survival from a randomized trial; and overall survival from a modeling study. There is a positive correlation, 0.9, between treatment episode prices and incremental survival benefits. A regression of the natural logarithm of prices on incremental life-years gained indicates that prices increase by

Figure 2
Drug Price per Life Year Gained versus Drug Approval Date
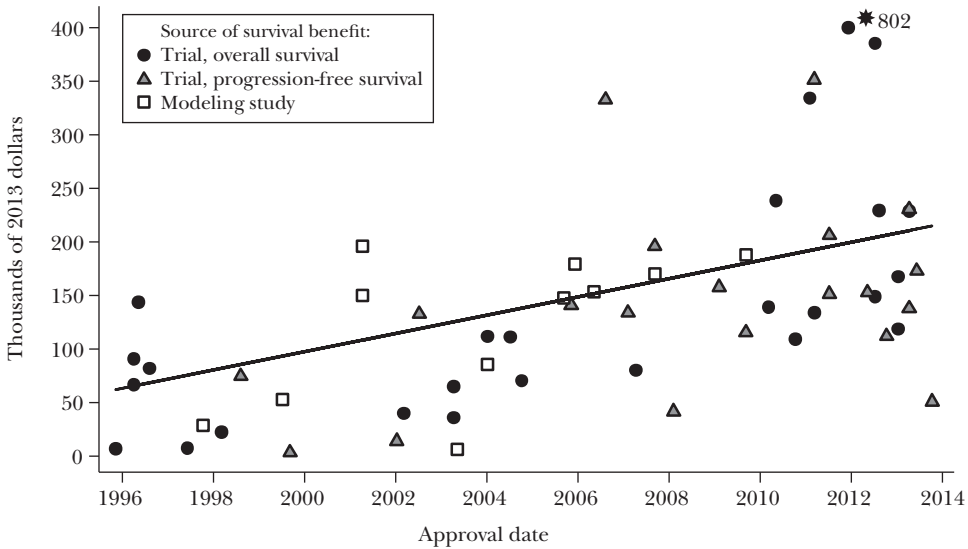
Source: Authors.
Notes: The best fit line is: Price per life year gained = $54,100 + $8,500 × Approval Year. Approval Year = 0 for 1995, 1 for 1996, . . . 19 for 2014. For purposes of display, we recoded one value from $802,000 to $400,000.

120 percent (with a 95 percent confidence interval ranging from 74 to 166 percent) for each additional life-year gained (or 14 percent per month gained). The effect in dollar terms is $75,000 per year gained (with a 95 percent confidence interval from $12,000 to $137,000).

Newer drugs are not associated with greater survival benefits compared to older drugs. A regression with life-years gained as the dependent variable and year of approval as the explanatory variable yields a small and insignificant coefficient (0.005 years of life gained, with a 95 percent confidence interval from −0.024 to 0.034 years of life gained).

Prices have increased over time. A regression of the natural logarithm of price on approval year indicates that prices increased by 12 percent per year (with a 95 percent confidence interval from 7 to 17 percent). The result is robust to the inclusion of a control for survival benefits.

For the remainder of the paper, we focus on trends in the price per life-year gained, which equals the price per treatment episode (in 2013 dollars) divided by survival benefits. The price per life-year gained can be thought of as a "benefit-adjusted" price. The sample average is $150,100 per year of life gained (with a standard deviation of $130,500). This value is in the range of estimates of the willingness-to-pay for a quality-adjusted life-year (Hirth, Chernow, Miller, Fendrick, and Weissert 2000). Figure 2 plots drugs' price per life-year gained against drugs'

approval date. There is an upward trend. A regression of the price per life-year gained on approval year indicates that benefit- and inflation-adjusted launch prices increased by $8,500 (with a 95 percent confidence interval from $2,900 to $14,100) per year.[5] The intercept (1995 is zero on the x-axis) is $54,100 (95 percent confidence interval: −$16,700 to $124,900). Put another way, in 1995 patients and their insurers paid $54,100 for a year of life. A decade later, 2005, they paid $139,100 for the same benefit. By 2013, they were paying $207,000.

Figure 3 shows trends in the price per life-year classified by different types of anticancer drugs. Upward trends are apparent for most disease types.

Price Per Life-Year Gained and Drug Attributes

We used least squares regression to determine if the relationship between the price per life-year gained (in 2013 dollars) and approval year is robust to the inclusion of controls for other drug attributes. Table 1 presents regression estimates (sample means and other summary statistics for the drug attributes are presented in the Appendix available at http://e-jep.org). We used the natural logarithm of the price per life-year gained as the dependent variable because the price per life-year gained is skewed. Results are qualitatively similar if we use untransformed prices as the dependent variable. Because of the modest sample size, we did not attempt to control for all drug attributes simultaneously.

The model in column A, the baseline specification, indicates that benefit- and inflation-adjusted launch prices increased 10 percent per year over the study period.

The model in column B adds controls for the gastrointestinal complication and neutropenia rates. The gastrointestinal (GI) complication rate is the average of the nausea, vomiting, and diarrhea rates experienced by patients on the drug. The neutropenia rate is the proportion of patients who experience high-grade neutropenia, a deficit of white blood cells which puts patients at risk of infection. We set missing values to "0." Data on the side effects experienced by patients in the control arms of trials are inconsistently reported. We controlled for absolute rather than relative side effect rates, which may be why the coefficient on the gastrointestinal complication rate is "wrong signed." In general, side effect rates are similar for newer and older drugs (Niraula et al. 2012).

The model in column C includes a control for administration route: intravenous versus oral. Oral drugs are more convenient for patients than physician-administered intravenous drugs, but patients' out-of-pocket costs are typically higher for oral drugs. The positive coefficient on the intravenous administration route is insignificant.

The model in column D explores the hypothesis that increases in prices reflect increased production costs. We test this hypothesis indirectly by examining the link between several proxies for production costs and prices. Biologic drugs are typically more expensive to develop and produce than traditional anticancer drugs.

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[5] The marginal effect from a generalized linear model with a log link and a gamma variance function is $8,500 (95 percent confidence interval: $1,800 to $15,300). Details of this approach are available in the online Appendix available with this paper at http://www.e-jep.org.

Figure 3
Drug Price per Life Year Gained versus Drug Approval Date by Indication
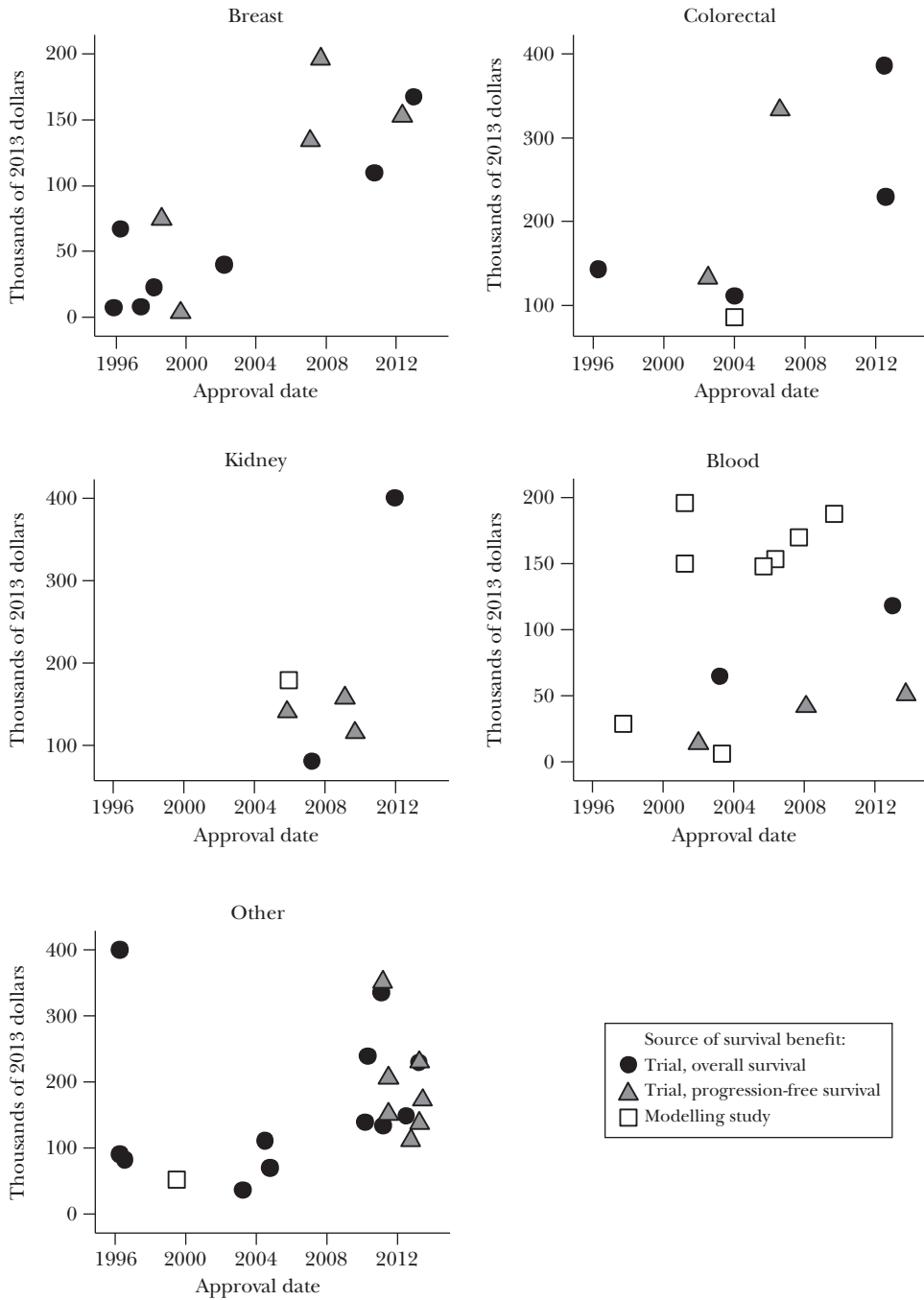
Source: Authors.

Table 1

Impact of Approval Year and Other Variables on the Natural Logarithm of the Price per Life Year Gained in 1,000s of 2013 US Dollars for 58 Cancer Drugs Approved between 1995 and 2013

	A	B	C	D	E	F
Approval year	0.10 [0.06, 0.14]*	0.10 [0.06, 0.14]*	0.10 [0.06, 0.14]*	0.10 [0.06, 0.15]*	0.10 [0.06, 0.15]*	0.09 [0.05, 0.13]*
GI complication rate		1.70 [0.47, 2.94]*				
Neutropenia rate		0.26 [−0.76, 1.28]				
IV drug			0.26 [−0.22, 0.74]			
Biologic				−0.15 [−0.67, 0.36]		
Multiproduct firm				0.38 [−0.14, 0.90]		
Randomized controlled trial					0.12 [−0.45, 0.69]	
Progression free survival					−0.36 [−0.91, 0.20]	
Placebo comparator						0.46 [−0.02, 0.94]+
Constant	3.51 [2.99, 4.03]*	2.95 [2.31, 3.59]*	3.34 [2.73, 3.95]*	3.24 [2.58, 3.89]*	3.48 [2.89, 4.06]*	3.39 [2.87, 3.92]*
R^2	0.28	0.37	0.29	0.31	0.30	0.32

	G	H	I	J	K
Approval year	0.10 [0.07, 0.14]*	0.10 [0.06, 0.14]*	0.09 [0.05, 0.14]*	0.09 [0.05, 0.13]*	0.11 [0.06, 0.15]*
Priority drug	0.93 [0.46, 1.40]*				
Orphan drug	−0.17 [−0.67, 0.33]				
Ln competitors		−0.64 [−0.99, −0.29]*			
Gene test			−0.59 [−1.05, −0.14]*		
Second line therapy			0.15 [−0.33, 0.62]		
Baseline survival				−0.29 [−0.53, −0.05]*	
Mortality rate					0.77 [−0.38, 1.92]
Constant	2.83 [2.23, 3.44]*	4.92 [4.01, 5.83]*	3.75 [3.09, 4.42]*	3.89 [3.30, 4.48]*	3.20 [2.50, 3.90]*
R^2	0.44	0.41	0.36	0.35	0.30

Notes: See text for definition of variables. 95 percent confidence intervals are in brackets. "GI" is gastrointestinal; "IV" is intravenous.
* Means significant at the 5 percent level, + means significant at the 10 percent level.

Multiproduct firms—firms that sell two or more anticancer drugs—are able to spread the fixed costs associated with marketing oncology drugs across products and may have equipment that can be used to manufacture two or more products. The coefficients on the cost-shifters are insignificant. These findings are consistent with the observation that there is a large gap between the generic and brand launch prices of anticancer drugs: for example, over 80 percent in the case of irinotecan (Conti et al. 2012). The prices of on-patent anticancer drugs do not appear to be closely related to marginal production costs.

The model in column E examines the relationship between the source of information about survival benefits and prices. We would expect that physicians would be more willing to prescribe drugs about which they have more information. This regression includes controls for whether the drug was approved on the basis of a randomized trial and if survival benefits are measured in terms of progression-free rather than overall survival. The coefficients are of the expected sign but are not significant.

The models in columns F–H consider whether drugs with few close substitutes command higher prices. Characterizing the degree of competition between anticancer drugs is difficult. Some compete, but most are used in a complementary manner, either in a co-administered multidrug "cocktail" regimen or in a sequence of therapy lines (first-line therapy, second-line therapy, etc.) Some drugs are approved to treat all patients diagnosed with late-stage cancer in a specific body part, while other drugs have narrower indications. The model in column F includes a control for whether the drug was compared against a placebo (or "best supportive care") or against another drug. Drugs tested against placebos occupy unique niches in the product space compared to drugs tested against "active" controls. Presumably the FDA and ethical review boards would not allow a manufacturer to test an anticancer drug against a placebo unless the drug had no direct substitutes. The coefficient is positive and significant at the 10 percent level. The model in column G includes controls for whether the drug was granted priority review status by the FDA. Priority review is granted to drugs that demonstrate "significant improvements in the safety or effectiveness of the treatment, diagnosis, or prevention of serious conditions when compared to standard applications." The model indicates that drugs awarded priority review status command significantly higher prices. The model in column H includes a variable equal to the natural logarithm of the number of drugs previously approved for the tumor site (National Cancer Institute 2014). The coefficient is negative and significant. It is unclear if this result can be interpreted as a purely competitive effect because anticancer drugs are often used in a complementary manner. The FDA grants orphan drug status to drugs used to treat rare conditions. The coefficient on orphan drug status (Model G) is not significant.

The model in column I includes controls for whether a drug was approved for use in patients with specific genetic biomarkers (US Food and Drug Administration 2014a) or as a second-line drug, for use in patients whose disease has progressed after an initial course of treatment. Demand may be less elastic, and prices higher, for drugs targeted at narrow patient subgroups. The coefficient on the gene test

variable is negative, contrary to our expectation. The discussion up until this point has implicitly assumed that patients' valuation of gains in life expectancy from a new anticancer drug is independent of how long they could expect to live if they do not receive a new drug. This approach treats anticancer drugs as bundles of comparable attributes. The model in column J includes a control for baseline survival (as measured by survival in the control or comparator arm of the study we used to assess survival benefits). Results indicate that the longer patients survive without the drug, the lower the drug price. Patients' and physicians' willingness-to-pay may depend on absolute survival as well as relative survival gains. They may place a higher value on a drug that extends survival time by 6 months from a base of 8 months than one that extends survival time by 6 months from a base of 12 months.

The model in column K includes a control for the tumor-specific mortality rate, which we calculated by dividing the number of deaths attributed to the tumor by disease incidence. The coefficient on the mortality rate is positive but is not significant.[6]

The coefficient on approval year is economically and statistically significant in all 11 specifications in Table 1. Thus, our basic finding that benefit- and inflation-adjusted launch prices increased by about 10 percent annually appears robust to the inclusion of controls for the various drug attributes described above.

Sensitivity Checks

We performed several sensitivity checks. We re-estimated the baseline model (column A) on the subsample of drugs approved on the basis of randomized trials and for which we had trial-based estimates of overall survival. We also re-estimated the baseline model on the subsample of drugs with prices below the 90th percentile ($94,000) to determine the sensitivity of results to extreme values. In both cases the coefficients on approval date indicate that prices increased by 10 percent annually and were significant at the 1 percent level, consistent with the results from the baseline model.

Explaining Pricing Trends

Our empirical results suggest that the launch prices of anticancer drugs, even when adjusted for inflation and survival benefits, have increased substantially over time. We offer two explanations grounded in our observations of market behavior, economic theory, and current regulatory policy.

Our discussion focuses on the launch prices of branded drugs. If manufacturers make large changes to drugs' prices in the years following launch, our focus may be misplaced. We analyzed the Average Sales Price files from the Center for Medicare

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[6] Mortality rates are measured with substantial error. Ideally, we would like to measure mortality among patients diagnosed with late-stage disease, but we do not have data on tumor incidence by stage at diagnosis.

and Medicaid Services for a subset of the drugs in our sample to determine if launch prices are a sufficient statistic for post-launch prices. The files capture prices for the mostly intravenous drugs reimbursed under Medicare's Part B outpatient medical benefit. We excluded three drugs—gemcitabine, irinotecan, and oxaliplatin—that experienced large declines in price following patent expiration and generic entry. We calculated annualized growth rates in the remaining sample of 19 drugs. The average annualized growth rate in real prices after launch was 1 percent. The 25th, 50th, and 75th percentiles were −0.7 percent, 0.9 percent, and 4 percent. The results are consistent with Lu and Comanor's (1998) finding that the prices of innovative drugs do not change much after launch. Launch prices are where the action is.

Reference Pricing

Writing to criticize the "astronomical" prices of new anticancer drugs, a group of over 100 prominent oncologists (Experts in Chronic Myeloid Leukemia 2013) proposed the following model of manufacturers' price setting behavior: "How are the prices of cancer drugs decided? Of the many complex factors involved, price often seems to follow a simple formula: start with the price for the most recent similar drug on the market and price the new one within 10–20 percent of that price (usually higher)." Industry insiders echo this theory of price-setting behavior. For example, from Hutchison (2010): "Gold [CEO of Dendreon] says that the cost of Provenge was based on the 'overall landscape' of treatment prices for cancer." From Marcus (2004): "A spokeswoman for AstraZeneca justified the price of Iressa as 'in line with other cancer treatments.'" From Silber (2005): "The retail price of the drug will be $5,416 per month, an amount that Onyx said is in the range of similarly specialized cancer drugs."

The theory that manufacturers set the prices of new drugs based on the prices of existing therapies (not necessarily competitors), rather than some intrinsic standard of product value, is consistent with reference price models of demand. Reference pricing models depart from the standard economic model of consumer behavior by allowing consumers' purchase decisions to depend on a pricing anchor, or reference price, rather than on an internal comparison of price and willingness-to-pay (Thaler 1985). Consumers may determine reference prices based on observed past prices or the prices of similar, but not necessarily substitute, goods.

Oncologists are in a strong position to influence the market share of anticancer drugs. Although oncologists do not face direct incentives to avoid costly drugs, they may balk at prescribing drugs with prices they perceive as exploitative—in the language of theory, drugs with prices above the reference price level. An extensive literature in economics and marketing describes how perceptions of fairness influence consumers' attitudes towards prices and market behavior (for example, Frey and Pommerehne 1993; Mas 2006; Maxwell 2002; Kahneman, Knetsch, and Thaler 1986; Piron and Fernandez 1995).

There is a "zone of indifference" around a reference price such that consumers ignore small deviations from the reference price (Kalyanaram and Little 1994). The zone of indifference gives manufacturers the ability to set the prices of new drugs

slightly above the prices of existing drugs without reducing quantity demanded. As costlier drugs come to market, oncologists become habituated to higher prices, giving manufacturers leeway to set even higher prices in the future. The characteristics of the market for anticancer drugs, including patent protection, which protects producers from direct competition, and generous third party payment, allow this dynamic to persist. These characteristics are present in other medical product markets but not to the same degree as in the anticancer drug market.

Over time, the use of reference prices leads to forward-looking price complementarities between manufacturers. When a new drug enters with a price in excess of the reference price, it re-establishes price levels, freeing up the next entrant to set its price even higher. Kahneman, Knetsch, and Thaler (1986) write, "[P]rice increases that are not justified by increasing costs are judged less objectionable when competitors have led the way." Shortly after the FDA approved bevazicimab and erlotinib, one Wall St. analyst noted: "Companies will be looking at these products to help them determine the pricing of their own drugs . . . Tarceva and other drugs will likely take their cue from Erbitux and Avastin" (Griffith 2004). According to textbook monopoly pricing theory, the price of Erbitux (generic name cetuximab) should have had no direct bearing on the price of Tarceva (generic name erlotinib), a lung and pancreatic cancer drug, because cetuximab was not a competitor at the time.

If a manufacturer sets a price that is perceived as exploitative, in the sense that the price exceeds the reference price to a large degree, it risks provoking a backlash. One example of where this happened involved a second-line treatment for metastatic colorectal cancer, ziv-aflibercept (brand name Zaltrap). When approved by the FDA in 2012, its price was double that of bevacizumab, its closest competitor, at bevacizumab's common dosing level. Oncologists did not view ziv-aflibercept as particularly innovative, and three prominent physicians at the Memorial Sloan Kettering cancer center wrote an opinion piece in the *New York Times* (Bach, Saltz, and Wittes 2012) stating that they would refrain from using ziv-aflibercept at their center because of its price. One month later the manufacturer, Sanofi, announced that it would provide purchasers with a 50 percent discount off the list price.

According to one Wall Street analyst, "market structure effectively provides no mechanism for price control in oncology other than companies' goodwill and tolerance for adverse publicity" (Anand 2007). The observation begs the question: What is to stop a manufacturer from setting the price of a drug at $1,000,000 or more? Drug manufacturers are able to set higher prices for new drugs, but they must be mindful of physicians' ability to exact retribution when manufacturers violate physicians' norms of fairness in pricing.

Required Pricing Discounts

Recent increases in the launch prices of anticancer drugs may be an unintended consequence of policies to expand access to price discounts. The so-called 340B drug pricing program, authorized by Congress in 1992, requires drug manufacturers to provide deep discounts to 340B-qualified buyers. At the program's inception, only

federally qualified health centers, specialized public health clinics, and "disproportionate share hospitals" (hospitals whose patient population includes a high proportion of low-income patients) qualified for 340B discounts. Discounts are set relative to the average price wholesalers, retail pharmacies, and providers pay manufacturers to purchase drugs, called the "Average Manufacturer Price." The 340B price discount for branded drugs must be at least 23.1 percent of the Average Manufacturer Price. Providers that purchase drugs through a government-designated distributor may receive additional discounts, though these are relatively small, totaling $67 million in 2013 (Drug Discount Monitor 2014). Participation in the 340B program is attractive for health care providers because they do not have to pass the discount on to insurers. They profit on the spread between third-party payers' drug reimbursement rates and the 340B discounted price.[7]

Since 1992, Congress and federal regulators have broadened eligibility to include critical access hospitals, free-standing cancer hospitals, some community hospitals, and outpatient clinics affiliated with disproportionate share hospitals. Mergers between 340B providers and non-340B providers, a predictable effect of the incentives inherent in the program, have also expanded the program's reach. Due to changes in eligibility rules and mergers, the number of providers in the 340B program increased from 8,605 in 2001 to 16,572 in 2011 (US General Accounting Office 2011). Industry sources predict that the volume of drug sales under the 340B program will increase from $6 billion in 2010 to $12 billion in 2016 (Biotechnology Industry Organization 2013).[8]

Because the 340B discount is based on a drug's average price, the program presents manufacturers with an incentive to set higher launch prices to offset discounts. Increases in the number of 340B-eligible providers have magnified the incentive, possibly leading to upward pressure in the prices paid by noneligible providers (Conti and Bach 2013). The 340B program also splits the market into price-elastic and price-inelastic segments. Just as branded drug manufacturers increase prices following generic entry to capture revenues from brand-loyal customers (Frank and Salkever 1997), manufacturers of recently launched drugs may cede large discounts to their price-sensitive segment but increase prices to non-340B providers.

The federal Medicaid program has its own set of drug pricing rules. In exchange for formulary coverage by state Medicaid programs, branded manufacturers give rebates to the federal government on sales to Medicaid patients. Similar to the 340B program, the rebate is based on the Average Manufacturer Price. If a manufacturer increases the price of a drug over and above the rate of inflation, it must pay a larger rebate. This aspect of the program provides incentives for firms to set higher prices initially, rather than increasing prices after launch. Although Medicaid

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[7] When calculating average sales prices for purposes of Medicare reimbursement, regulations instruct manufacturers to exclude sales to 340B providers. Hence Medicare reimbursement rates are not affected by growth in the 340B discount program, though providers' acquisition costs are reduced.
[8] This figure includes anticancer and noncancer drugs. Industry sources indicate that the two therapeutic classes having the largest 340B sales are anticancer drugs and anti-infectives.

accounts for less than 10 percent of spending on cancer treatment (Howard, Molinari, and Thorpe 2004), enrollment in the program is growing, presenting manufacturers with additional incentives to increase prices to non-Medicaid patients.

The United Kingdom and other European countries negotiate drug prices with manufacturers. Although negotiated discounts are not legislatively linked to the US price, the US price may serve as an opening bid in negotiations, and discounts are often expressed as a percent of the US list price in contracts. As pressure has mounted on governments to reign in health spending, European health systems have adopted a more aggressive bargaining stance, backed by a credible threat of noncoverage, potentially leading manufacturers to set higher US prices.[9] The United Kingdom and many other countries do not divulge negotiated drug prices, and so we are unable to determine whether launch prices have increased outside the United States. There is anecdotal evidence that they have. For example, a number of signatories to a statement calling attention to the "unsustainable" prices of new anticancer drugs were European physicians (Experts in Chronic Myeloid Leukemia 2013).

Other Potential Causes of Price Increases

What about other possible explanations for pricing trends, such as shifts in patient or physician demand? Changes on the demand side of the market seem inconsistent with observed pricing trends. The income elasticity of the demand for health care is not large enough to account for changes in prices or health care spending generally (Newhouse 1992). Moreover, patient cost-sharing is higher now than it was in 1995 as consumers have shifted to high-deductible plans (Berndt and Newhouse 2012; Kaiser Family Foundation 2013). The structure of insurers' payments to physicians has remained largely unchanged, but payment levels for physician-administered anticancer drugs have declined following passage of the Medicare Modernization Act in 2003 (Jacobson et al. 2006; Jacobson, Earle, Price, and Newhouse 2010).

On the supply side, it is unlikely that changes in development and production costs alone can explain launch pricing trends. The FDA has reduced barriers to approval, and advances in genetics have facilitated drug discovery. The generic versions of anticancer drugs cost much less than the branded versions, suggesting that production costs are low relative to pre-patent expiration price levels. Pharmaceutical manufactures often claim that they set drug prices to recoup research and development costs. Manufacturers' research and development costs may have increased over time. As more drugs come to market, the number of unexploited targets for anticancer therapy shrinks, requiring firms to invest more to develop new drugs. Lacking measures of research and development costs, we are unable to evaluate the claim empirically. However, research and development costs are sunk

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[9] The British National Health Service and other national health systems do not disclose negotiated prices, and so we cannot determine whether the spread between domestic and international drug prices has increased.

at the time of product launch and so they ought not to factor into the pricing decisions of a profit-maximizing firm once the product has been developed. We believe the direction of causation runs from prices to research and development costs—as prices increase, manufacturers are willing to spend more to discover new drugs—rather than the other way around.

Discussion

We find that, controlling for inflation and survival benefits, the launch prices of new anticancer drugs have increased over time. We do not anticipate that US payers and providers will change their policies in a way that will fundamentally change pricing dynamics, at least in the near term. The American Society of Clinical Oncology, the main professional group for physicians who treat cancer patients, is encouraging its members to consider costs when they choose drugs, but these efforts are mostly focused on costs to patients rather than systemwide costs. Efforts to increase the sensitivity of physician demand to drug prices still rely on physicians' sense of fairness rather than their pocketbooks. A Congressional advisory board, the Medicare Payment Advisory Commission, recently held a hearing on reforming reimbursement for physician-administered drugs. Many committee members voiced support for proposals that would reduce Medicare reimbursement for drugs if there are less-costly alternatives that have a "similar health effect" (InsideHealthPolicy 2014). However, newly-approved anticancer drugs are, by definition, unique, and will probably be unaffected if Medicare implements the policy.

To supporters of the US health care system, new anticancer drugs are a potent symbol of progress and represent the type of innovation that would be squelched if Medicare and other US insurers denied coverage to costly treatments (for example, Gingrich 2009). To critics, the pricing of new anticancer drugs represents the worst excesses of a system that provides few checks on drug companies' pricing power and prioritizes gains in health, however small, over cost control. Policymakers are quick to agree that the health system should discourage use of ineffective treatments, but it is unclear how regulators, insurers, and physicians should approach treatments that are more costly but also offer small incremental benefits.

The optimistic view of recent trends in cancer drug development is that although individual drugs may not be associated with large gains in survival, the work that goes into developing a new drug contributes to the stock of knowledge about cancer biology. Eventually, scientists will use the information gleaned from the development of existing drugs to develop new drugs with much greater benefits. The pessimistic view is that current coverage, reimbursement, and patent policies (Budish, Roin, and Williams 2013) divert drug manufacturers' attention away from developing drugs that yield truly meaningful survival benefits. If insurers restricted coverage to drugs that improved survival time by an economically significant amount, perhaps there would be more of them.

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