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Steady Increase In Prices For Oral Anticancer Drugs After Market Launch Suggests A Lack Of Competitive Pressure

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ABSTRACT The cost of treating cancer has risen to unprecedented heights, putting tremendous financial pressure on patients, payers, and society. Previous studies have documented the rising prices of cancer drugs at launch, but less critical attention has been paid to the cost of these drugs after launch. We used pharmacy claims for commercially insured individuals to examine trends in postlaunch prices over time for orally administered anticancer drugs recently approved by the Food and Drug Administration (FDA). In the period 2007–13, inflation-adjusted per patient monthly drug prices increased 5 percent each year. Certain market changes also played a role, with prices rising an additional 10 percent with each supplemental indication approved by the FDA and declining 2 percent with the FDA's approval of a competitor drug. Our findings suggest that there is currently little competitive pressure in the oral anticancer drug market. Policy makers who wish to reduce the costs of anticancer drugs should consider implementing policies that affect prices not only at launch but also later.

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Rapid scientific progress in molecular and genomic science in the past few decades has fueled tremendous advances in anticancer medications.[1] These new drugs and biological agents in many cases represent a paradigm shift in oncology and can sometimes offer substantial health benefits to patients. However, they have also contributed to the rapidly rising cost of cancer treatment in the United States.[2–5] Concerns that the rising cost of drugs for cancer treatment is placing tremendous financial pressure on patients, payers, and society have been raised by the popular press and discussed in academic and clinical publications.[6–9]

Previous studies have documented the rapidly rising prices of cancer drugs at launch and largely attributed these trends to the recent advances in basic science, patent protections that incentivize pharmaceutical research and development, and insurance regulations that govern the coverage of chemotherapy in private and public settings and severely limit insurers' ability to negotiate with drug manufacturers.[2,10–12] To our knowledge, however, no study has comprehensively examined trends in the cost of anticancer medications after their initial approval by the Food and Drug Administration (FDA).

The costs of developing and bringing a new pharmaceutical product to market are large, but the marginal costs of production are generally very small. By granting manufacturers a temporary monopoly, patent protection preserves the financial incentives for pharmaceutical firms to invest in research and development and to invent new drugs. Because the marginal production costs for pharmaceutical products are relatively low, pharmaceutical firms have strong incentives to increase demand.

An important mechanism for increasing demand for anticancer medicines is the receipt of supplemental approvals from the FDA. For ex-

ample, imatinib was initially approved in 2001 to treat certain adults with chronic myeloid leukemia,[13] but it has since been approved for ten additional indications, including gastrointestinal stromal tumors[14] and pediatric chronic myeloid leukemia.[15] Importantly, if a drug's receipt of supplemental FDA indications generates additional demand, it would also be expected to increase the drug's price.

Most pharmaceutical products have near-monopoly status for the life of a patent or until a similar product enters the market. The recent example of Gilead's Harvoni (ledipasvir and sofosbuvir) and AbbVie's Viekira Pak (ombitasvir, paritaprevir, and ritonavir tablets copackaged with dasabuvir tablets) as treatment for hepatitis C indicate that the introduction of a competitor product can lead to substantial price concessions. However, anecdotal evidence suggests that competition has not appreciably lowered drug prices in oncology.[6] For instance, despite the introduction of several similar drugs, the price of imatinib has continued to climb since its initial approval. To our knowledge, there is little empirical evidence about the effect of a new product's entry on the price of similar anticancer drugs.

Understanding how market conditions influence cancer drug costs is critical to developing effective policies to address these growing costs. Our objective was to describe changes over time in the monthly costs for orally administered cancer drugs recently approved by the FDA and to examine whether and how those changes were associated with the receipt of additional indications and the introduction of competitors.

Study Data And Methods

STUDY SAMPLE Using National Drug Codes, we identified pharmacy claims from the Truven Health MarketScan Commercial and Medicare Supplemental Databases for orally administered medications approved by the FDA in the period 2000–12 to treat cancer. We excluded claims for patients being treated with cancer-related drugs for noncancer conditions (such as everolimus, to prevent organ rejection). The MarketScan databases represent the individual-level health services records of approximately 150 million individuals with commercial or Medicare supplemental coverage through privately insured fee-for-service, point-of-service, or capitated plans.

AVERAGE THIRTY-DAY PAYMENTS As a proxy for monthly drug costs, we calculated average per patient payments for a thirty-day supply of each drug in each quarter in the period 2007–13. To account for potential changes in dosing over time, we also calculated average payments per milligram in each quarter, which we considered a proxy for drug prices. Expenditures for each drug were calculated as the payments from both patients (copayments and coinsurance) and the health plan. Payments from the health plan represented the amount paid after applying relevant manufacturers' discounts.

We log-transformed payments, although our findings were very similar if we analyzed absolute costs directly (for results of sensitivity analyses using absolute costs, see online Appendix Exhibit A1).[16] All costs were adjusted for inflation to 2014 dollars using the Consumer Price Index.

We excluded one drug (cabozantinib) from our analyses because there were too few claims to allow us to calculate robust estimates of average drug costs. This exclusion made no difference to our results.

MEASURING CHANGES OVER TIME IN THE MARKET FOR A DRUG In oncology the majority of new drug applications or biologic licensing applications are in pursuit of FDA approval for a specific patient population and indication. And in oncology these indications are frequently for patients with advanced disease or disease progression following initial treatment. Once a drug is approved for the initial patient population and indication, its manufacturer often seeks supplemental approvals for additional indications. Once approved by the FDA, they are included in the product's label and collectively referred to as "labeled indications."

First, we hypothesized that supplemental FDA approval for a drug would be associated with an increase in average monthly drug costs by strengthening the monopoly status of the manufacturers, increasing demand for the drug, or both. We also explored how changes in the number of individuals diagnosed with a clinical condition for which the drug was newly indicated were associated with changes in costs.

Second, we hypothesized that a new indication for a larger number of individuals would translate into greater increases in drug costs than a new indication for a smaller patient population. We used data from the Surveillance, Epidemiology, and End Results (SEER) Program to estimate the approximate number of patients newly diagnosed with each cancer condition, and we used the published literature to adjust these estimates to more closely align with each drug's FDA-approved labeled indication (for example, the proportion of patients with a particular genomic marker). We considered these adjusted SEER estimates to be a reasonable approximation of the incremental annual incidence in the United States of the patient population for which the drug was newly indicated with each supplemental indication.

After initial FDA approval, physicians also can prescribe products "off label." In oncology off-label prescribing is widespread and frequently covered by insurers when the indication is included in a compendium (a resource that lists the medically accepted off-label uses of drugs and biologics), as a result of legislation that requires Medicare and Medicaid to cover off-label uses of anticancer drugs and biologics if the uses are included in certain compendia.[17–20] We therefore also examined whether compendia-listed indications for cancer-related conditions other than the labeled indications were associated with changes in average monthly costs for a drug over time. We obtained FDA-approved indications from each drug's label[21] and a list of compendia-recommended off-label indications that were given a class IIb recommendation (meaning that the drug is recommended in some cases), a class IIa recommendation (meaning that it is recommended in most cases), or a class I recommendation (meaning that it is recommended) from the Micromedex 2.0 DRUGDEX compendium.[22] We also obtained from Micromedex the dates that evidence was first reviewed and found to support these off-label recommendations.

Lastly, we hypothesized that the introduction of a new drug or biologic product to treat the same condition as one of the drugs in our sample would be associated with a decrease in drug costs by improving health insurers' leverage in negotiations with manufacturers, reducing patient demand, or both. We obtained a list of all drugs approved for different cancer sites from the National Cancer Institute[23] and associated dates of indication-specific FDA approval from the Drugs@FDA database.[24] Additional details on our pragmatic categorization of competitor products are available in the Appendix.[16]

STATISTICAL ANALYSES We used fixed effects regression models to evaluate whether and how changes in the factors described above were associated with changes in average monthly drug costs or prices. Fixed effects models control for all fixed drug characteristics (such as price at launch) and thereby produce slope parameter estimates that are derived from the variation of the independent variables within each drug over time.

We estimated standard errors that were robust to autocorrelation, heteroskedasticity, and cross-sectional correlation.[25] The numbers of supplemental FDA approvals, off-label indications, and competitor entries in each quarter were included in our regression models as time-varying covariates. All statistical analyses were performed in Stata, version 14.0.

LIMITATIONS Our study had a number of limitations that warrant discussion. First, the adjudicated payment data from the MarketScan Commercial and Medicare Supplemental databases do not contain a record of couponing or other drug assistance programs, which could lower the real costs borne by patients. However, patients paid a relatively small proportion of total costs (less than 2 percent of total monthly drug costs, on average), so this limitation should not affect our main conclusions.

Second, we used the dates on which evidence was reviewed in support of a new off-label indication in Micromedex DRUGDEX as a proxy for the date a drug was recommended for off-label use. However, the use of anticancer drugs off label is likely driven by multiple compendia recommendations, as well as the original literature on which the compendia based their recommendations. Thus, the timing of an off-label recommendation may be difficult to attribute to a single quarter.

Third, it is possible that our results regarding off-label indications would have been different if we had used an alternative compendium. However, a review found that Micromedex DRUGDEX had the most comprehensive listing of off-label indications and the most up-to-date evidence supporting these indications of five drug compendia, including that of the National Comprehensive Cancer Network.[17]

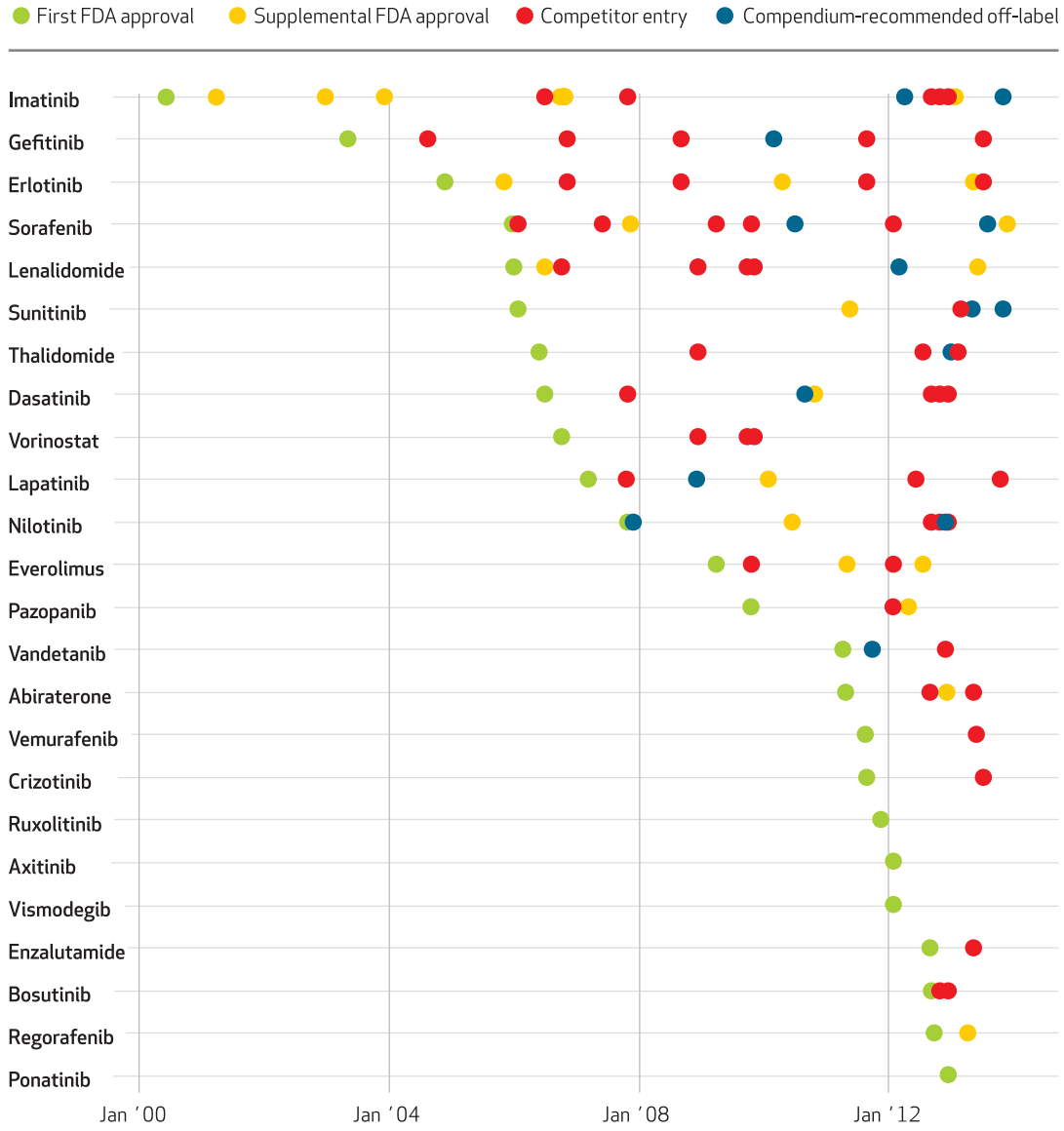
Study Results

We analyzed twenty-four drugs and 403 quarter-years of observations (Exhibit 1). In the period 2007–13, thirty-day costs for these drugs increased, on average, 5.2 percent per year (95% confidence interval: 3.8, 6.5) after initial market introduction, after adjustment for inflation. We observed substantial heterogeneity over time and across drugs with respect to the changes in costs. For example, the monthly cost of sunitinib exhibited both a 9 percent decrease and a 15 percent increase from one quarter to the next during the study period (Exhibit 2).

We found several important associations between changes in the market for a drug and average monthly costs. After adjusting for the average increase in costs over time above inflation, we found that the receipt of a supplemental approval by the FDA was associated with a significant 9.9 percent (95% CI: 4.4, 15.7) increase in per patient monthly costs and that the receipt of a compendium-recommended off-label indication was associated with a nonsignificant 3.2 percent (95% CI: −0.4, 6.9) increase. In contrast, FDA approval of a competitor product was associated with a significant 2.4 percent (95% CI: 0.4, 4.5) decrease in average monthly costs. Our findings were similar when we included all

EXHIBIT 1

Timelines for FDA approval of orally administered anticancer drugs



SOURCE Authors' analysis of data from the following sources: (1) Dates of initial Food and Drug Administration (FDA) approval, supplemental labeled indications, and FDA approval of a competitor product from the Drugs@FDA database (see Note 24 in text). (2) Dates that evidence was reviewed to support off-label indications from Micromedex (see Note 22 in text).

variables in a multivariable model (Exhibit 3).

Lastly, we found that larger increases in the size of the annual incident patient population for which the drug was newly indicated were associated with larger increases in per patient monthly costs. Specifically, for each additional 1,000 patients, the per patient monthly costs rose 18.8 percent (95% CI: 9.0, 29.6).

We also evaluated trends in drug prices per milligram instead of in monthly drug costs to assess whether our results were robust to potential changes in the average dose being administered to patients over time. Compared to our analyses of monthly costs, we found a similar association between price per milligram and the introduction of a competitor product (a 2.2 percent decline in price) and the receipt of a supplemental FDA approval (a 10.0 percent increase) (Exhibit 4). However, we found no significant association with a compendium-recommended off-label indication.

To further explore the differences in our results using monthly costs versus prices per milligram, we also evaluated how average pre-

EXHIBIT 2

Trends in average costs for a thirty-day supply of sunitinib

SOURCE Authors' analysis of data from pharmacy claims for 2007–13 from the Truven Health MarketScan Commercial and Medicare Supplemental Databases. **NOTE** Similar figures for all other drugs included in our analysis are available in the Appendix (see Note 16 in text).

scribed daily doses have changed over time (Appendix Exhibit A2).[16] We found a small but significant decline in the average daily dose being prescribed over time (<1 percent per quarter; $p = 0.002$). We found no evidence that the receipt of a supplemental FDA approval or the introduction of a competitor was associated with average daily doses being prescribed. However, we did observe a 4.9 percent (95% CI: 1.5, 8.4) increase in the average daily dose with each off-label indication.

Thus, our results regarding the effect on monthly costs of the receipt of a supplemental FDA approval and the introduction of a competitor were robust to potential changes in the dose being prescribed to patients over time. In contrast, our findings regarding the effect of compendium-recommended off-label indications appear to be mediated by such changes.

We performed several sensitivity analyses to assess the robustness of our results. Our conclusions were similar when we used absolute instead of log-transformed costs (Appendix Exhibit A1).[16] Nor did the results change importantly if we used median costs instead of average costs as the outcome variable (Appendix Exhibit A3),[16] which indicated that our results were not unduly influenced by some extreme values at the individual-claim level.

We also explored how the changes we observed in drug costs were being borne by payers and patients separately. We found no evidence that average payments by patients for anticancer drugs had increased over time or were affected by the introduction of a competitor or an additional off-label indication (Appendix Exhibit A4).[16] In contrast, our findings using only reimbursements from health insurers were very similar to our main results (Appendix Exhibit A5).[16]

Lastly, we found similar results when we repeated our analyses using quarterly data on drug utilization and Medicaid prescription drug payments from the Medicaid State Drug Utilization Data National Summary Files. These aggregated data on drug payments do not include rebates from manufacturers and therefore reflect trajectories in list prices. After initial market introduction, average per patient payments from Medicaid for a thirty-day supply of the anticancer drugs included in our main analyses increased 6.1 percent per year (95% CI: 5.7, 6.5) (Appendix Exhibit A6).[16] We found similar impacts on per patient Medicaid reimbursements with each additional off-label indication and the introduction of a competitor.

Discussion

We used a large commercial claims database to examine recent trends in monthly costs for oral anticancer drugs recently approved by the FDA. Overall, we found substantial increases in monthly costs for these drugs over time, as well as important differences in changes over time and across drugs. Our findings support our hypotheses that specific changes in the pharmaceutical market are associated with changes in drug costs over time. Specifically, per patient costs rose after a drug received supplemental indications from the FDA and decreased slightly with the introduction of a competitor drug. Payment models and policies designed to address the rapidly rising costs of oral anticancer drugs will therefore need to address not only rising launch prices, but also the rapidly rising costs of these

EXHIBIT 3

Change in costs for a thirty-day supply of oral anticancer drugs recently approved by the FDA, 2007–13

Change after:	Change in costs	95% CI	*p* value
Additional supplemental indication	9.2%	4.3, 14.3	0.001
Additional compendium-recommended off-label indication	4.3	0.0, 8.9	0.061
FDA approval of a competitor drug	−1.8	−3.1, −0.4	0.003
One year	4.4	3.1, 6.0	<0.001

SOURCE Authors' analysis of data from pharmacy claims from the Truven Health MarketScan Commercial and Medicare Supplemental Databases, Food and Drug Administration (FDA) approval dates, and off-label compendium listings in Micromedex (see Note 22 in text). **NOTES** The exhibit shows multivariable regression model coefficients for log-transformed average costs for a thirty-day supply, as measured in each quarter between the first quarter of 2007 and the fourth quarter of 2013 after the drugs were approved by the FDA. A variable for the size of the indicated patient population was not included in the multivariable model because it was highly correlated with receipt of a supplemental FDA indication. CI is confidence interval.

EXHIBIT 4

Change in price per milligram of oral anticancer drugs recently approved by the FDA, 2007–13

Change after:	Change in price	95% CI	*p* value
Additional supplemental indication	10.0%	3.9, 16.7	<0.001
Additional compendium-recommended off-label indication	–0.5	–4.0, 3.4	0.8
FDA approval of a competitor drug	–2.2	–3.0, –1.4	<0.001
One year	7.1	5.8, 8.3	<0.001

SOURCE Authors' analysis of data from pharmacy claims from the Truven Health MarketScan Commercial and Medicare Supplemental Databases, Food and Drug Administration (FDA) approval dates, and off-label compendium listings in Micromedex (see Note 22 in text). **NOTES** The exhibit shows multivariable regression model coefficients for log-transformed average price per milligram, as measured in each quarter between the first quarter of 2007 and the fourth quarter of 2013 after the drugs were approved by the FDA. A variable for the size of the indicated patient population was not included in the multivariable model because it was highly correlated with receipt of a supplemental FDA indication. CI is confidence interval.

drugs after their initial FDA approval.

Other researchers have documented the growing expenditures for oral chemotherapy and found that, in the aggregate, such spending has grown dramatically in recent years. For example, Erin Trish and colleagues found that the growing use of oral chemotherapy was the largest driver of increased spending on specialty drugs among Medicare and Medicare Advantage enrollees.[26] Ya-Chen Tina Shih and colleagues reported that insurance payments per patient per month for targeted oral anticancer medications more than doubled in ten years, and that the overall growth in drug prices occurred both at launch and in the years after launch.[27] Our findings of substantial growth in oral anticancer drug prices after launch corroborate these results and add a more detailed analysis of these trends at the level of individual drugs.

Our findings also corroborate previous studies by Peter Bach and colleagues that have reported substantial increases in the launch prices of new drugs.[2,28] However, our results differ with respect to describing postlaunch changes in prices for specific drugs over time. Whereas David Howard and coauthors recently reported that the prices of new anticancer drugs did not change substantially after launch,[28] we observed large overall increases in real monthly prices in the years following a drug's launch, as well as substantial variability across drugs and time in those trends. These discrepancies may be explained by the drugs included in the analyses: Howard used an unspecified subset of nineteen drugs, most of which were intravenously administered, while our analyses included almost all of the orally administered drugs approved by the FDA between 2000 and 2012.

In 2013 a group of more than a hundred experts on chronic myeloid leukemia published an article in *Blood* to call attention to the rapidly rising cost of cancer drugs, particularly the tyrosine kinase inhibitors used to treat chronic myeloid leukemia.[6] The authors noted that the price of imatinib had increased from nearly $30,000 when it was launched in 2001 to just over $90,000 in 2013.

We observed very similar trends in the price of imatinib. Importantly, we also found that these trends were not consistent over time: In some quarters, the price of imatinib climbed more than 8 percent, whereas in others it remained constant or even declined very slightly (Appendix Exhibit A7).[16] Moreover, these trends were associated with specific changes in the market for imatinib that closely mirrored our main findings: The price decreased slightly with the introduction of a competitor and increased faster following the receipt of a supplemental FDA indication. The authors of the *Blood* article concluded by calling on all parties concerned to begin to address the reasons behind rising cancer drug prices and offer ways to reduce the prices. We believe that the findings we have presented here identify some of the factors associated with rising cancer drug prices after launch and can therefore help guide the development of potential solutions and sound policies.

Implications

We found that the monthly cost of orally administered anticancer drugs increased, on average, 5 percent per year above inflation in the years after FDA approval. These trends may worry policy makers, given the large market for oral chemotherapy and the concurrent increase in launch prices for these drugs that shows no sign of abating. That said, these drugs can offer substantial health benefits to patients, and the extent of these benefits may not be fully apparent at the time the drug is first approved by the FDA. Further work is needed to understand how the evidence regarding the clinical benefits of these drugs changes over time, both within and across indications, and whether these changes are associated with the pricing trends we observed.

Our results show that with each supplemental indication received, monthly drug costs increase over and above the average inflation-adjusted rise in costs over time. If a supplemental indication offers a larger clinical benefit for patients than the original indication, it may be reasonable to pay a higher price for the drug than initially negotiated. However, if the supplemental indication offers a smaller benefit for newly indicated patients than those receiving the drug under the original indication, then higher prices across the board are not justified.

We also found that the introduction of a competitor product exhibited a relatively small effect (a 2 percent decrease) on monthly drug costs. The likely explanation is that competition among manufacturers has been effective in controlling prices for drugs in many chronic conditions, but it has largely been unsuccessful in oncology.[11] Cancer patients often are treated with multiple lines of therapy until all options are exhausted, so the choice of one drug does not necessarily preclude the concurrent or subsequent demand for other similar drugs.

In other words, the way in which new cancer drugs are tested and used in practice produces an effective monopoly that does not end with the introduction of a competitor product. Drugs can therefore have whatever prices the market will bear—which can be extraordinarily high when an insured person faces a life-threatening illness.[28] Moreover, current regulations largely prevent Medicare and many health plans that fall under state regulatory authority from categorizing cancer drugs with related chemical structures and indications as interchangeable, which further limits competitive pressure in the oncology drug market.[2]

Our findings therefore suggest that competition is unlikely to meaningfully rein in the escalating costs of oral anticancer drugs in the near future. Instead, potential policies to address these trends could seek to link reimbursement rates or coverage mandates with a metric of comparative clinical value or benefit.[29–31] That would ensure patients' access to effective therapies while leaving insurers some leverage in negotiations with manufacturers. A first step toward implementing such a system would be to define the clinical benefit or value of new cancer treatments in a standardized and transparent manner—a process that has gained substantial momentum with the development of the American Society of Clinical Oncology's value framework,[32] Memorial Sloan Kettering's DrugAbacus tool,[33] and other efforts.[34]

Importantly, we believe that policies to link coverage to the value of cancer treatments would need to be linked in turn to an indication-specific reimbursement system, either at the patient or population level (for instance, using a "blended" reimbursement in which the weighting was linked to the indication-specific sales volume of a drug), given the tremendous range in value of a cancer treatment across indications.[35] Efforts to link prices for cancer drugs with evidence on how well they work for an indication are under way within the private sector in the United States.[36] However, these efforts are still in their infancy, and we believe this area warrants additional study and attention.

We did not look at the effect of losing patent protection because all of the drugs in our analyses remained under patent protection throughout the study period. Using data from 2000–07, Rena Conti and Ernst Berndt found that the decline in prices for oral cancer drugs was much lower than that for physician-administered formulations after a generic competitor entered the market.[37] If this effect persists, generic entry is also unlikely to offer substantial respite from these rising costs. That said, some experts believe that the market entry of generic imatinib, expected in 2016, will have a profound impact on the price of the drug and possibly on the prices of other second-generation tyrosine kinase inhibitors as well.[38] It will therefore be important to revisit the effect of generic entry on oral cancer drugs once data on expenditures are available after the arrival of generic versions of imatinib and other drugs included in these analyses.

Conclusion

Using data on a large population of commercially insured patients, we observed substantial increases in the average per patient monthly costs of oral anticancer medications approved by the FDA in recent years. The underlying factors driving these trends are likely complex. Our results help shed light on the important association between several changes in the market for newer oral cancer drugs over time—most notably, the introduction of a competitor drug and the receipt of supplemental FDA approvals—and changes in per patient expenditures for these drugs. Whether the increasing expenditures that were associated with additional indications represent higher demand or more effective use of monopoly status warrants further exploration. ■

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