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ORIGINAL REPORT

Association of Patient Out-of-Pocket Costs With Prescription Abandonment and Delay in Fills of Novel Oral Anticancer Agents

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ABSTRACT

Purpose
The number of novel oral anticancer agents is increasing, but financial barriers may limit access. We examined associations between out-of-pocket (OOP) costs and reduced and/or delayed treatment initiation.

Methods
This retrospective claims-based study used 2014 to 2015 data from a large, proprietary, integrated database and included Medicare and commercial insurance enrollees with a new, adjudicated prescription for any of 38 oral anticancer agents. We examined rates of claim reversal (failure to purchase approved prescription), delayed initiation (reversal with subsequent fill of same agent within 90 days after adjudication), and abandonment (reversal with no fill of same agent within 90 days after adjudication) for the index oral anticancer agent. We also examined whether patients filled any alternate oral, injectable, or infusible anticancer agent within 90 days. Logistic regressions controlled for sociodemographic, clinical, and treatment characteristics to estimate adjusted rates.

Results
Among the final sample (N = 38,111), risk-adjusted rates of claim reversal ranged from 13% to 67%, increasing with higher OOP costs. Although the abandonment rate was 18% overall, risk-adjusted rates were higher in greater OOP cost categories (10.0% for ≤ $10 group *v* 13.5% for $50.01 to $100 group, 31.7% for $100.01 to $500 group, 41.0% for $500.01 to $2,000 group, and 49.4% for > $2,000 group; $P < .001$ compared with ≤ $10 group). Rates remained similar after accounting for use of alternate oral, injectable, or infusible anticancer agents. Delayed initiation was also more frequent for higher OOP cost categories (3% in ≤ $10 group *v* 18% in > $2,000 group; $P < .001$). Sensitivity and subgroup analyses by insurance type, pharmacy type, sex, and indication identified similar associations.

Conclusion
Higher OOP costs were associated with higher rates of oral prescription abandonment and delayed initiation across cancers. Fiscally sustainable strategies are needed to improve patient access to cancer medications.

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INTRODUCTION

The number of novel oral anticancer therapies has increased considerably in recent years, and federal investment in the Cancer Moonshot initiative is poised to generate more advances. In addition to expanding treatment options, use of oral anticancer agents has led to corresponding shifts in insurance coverage and care delivery. First, whereas older intravenous therapies are covered under a patient's medical benefit, oral agents are typically covered under a pharmacy benefit. Second, as a result of higher prices, novel oral agents are frequently placed on specialty tiers that carry substantial out-of-pocket (OOP) costs (ie, copayments or coinsurance).[1-3] Third, because the entire OOP obligation for an oral prescription is due up front (at the time it is obtained from the pharmacy) rather than after medical services are rendered, high OOP costs confer a unique risk of delayed access or treatment abandonment. Given that prompt initiation is often critical for optimal outcomes, clarification of the relationship between high OOP costs and treatment initiation is urgently needed.

ASSOCIATED CONTENT

Appendix
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Most prior studies examining this relationship[4-7] have used insurance claims data that included information on filled prescriptions only. Hence, they were unable to determine whether noninitiators did not receive a prescription or whether they received a prescription but did not fill (purchase) it. One published study with more complete information, examining 10,508 patients with Medicare or commercial insurance who were prescribed one of eight oral anticancer agents from 2007 to 2009, found that 10% of all patients with a prescription abandoned that initial prescription and did not fill a substitute oral prescription in the subsequent 90 days.[8] Individuals with OOP costs > $500 for the initial prescription were found to have four times greater odds of abandoning their prescriptions, compared with those with OOP costs ≤ $100.

We sought to assess financial barriers to treatment by examining the association between OOP costs and initiation of novel oral anticancer agents indicated for a wide range of cancers. We built on past research in five ways. First, we examined recent data (2014 to 2015) that reflect increasing trends toward high cost sharing in both commercial and Medicare Part D prescription drug plans. Second, this time frame allowed us to examine 38 available oral anticancer agents. Third, we examined time to initiation for those who filled their prescriptions to examine delays in treatment. Fourth, we captured whether those who abandoned their initial oral anticancer agent filled an alternate oral agent or infusible anticancer agent over the next several months. Fifth, we repeated our analyses in several subgroups of interest (by insurance type, pharmacy type, sex, and indication).

METHODS

Data Source

We acquired data from 2014 to 2015 from Symphony Health Solutions' Integrated DataVerse (Conshohocken, PA).[9] This large, proprietary database contains claims from > 270 million active patients in the United States, including all insurance types and each US state. The age, sex, and regional distributions of patients in the data set are similar to the US census distributions.[10] The database also includes point-of-sale prescription purchase information detailing the patient's OOP liability (after application of coupons or copay assistance) and final claim payment status (paid or reversed claim). This unique combination—inclusion of patients across insurance segments and detailed prescription life cycle data—is typically not available in traditional insurance claims data sets (eg, Medicare claims).

The database links patient-level data obtained from providers through three sources: switch/network (clearinghouse) transactions, pharmacy point-of-service, and additional direct prescription, medical, and hospital claims. To allow for longitudinal tracking, claims for each patient are linked across data sources (eg, pharmacy, hospital) and de-identified, using unique encrypted identifiers in compliance with the Health Insurance Portability and Accountability Act. The database has been used in numerous prior studies in oncology[11,12] and other disease areas.[13-16]

Study Design and Sample

Our observational cross-sectional analysis examined the association between OOP costs and initiation of novel oral anticancer agents. Patients were included if they had a new, adjudicated pharmacy claim (ie, a payer-approved prescription, including determination of the insurance plan's payment and the OOP cost owed by the patient) for an oral anticancer agent (index prescription/index agent) between July 1, 2014, and June 30, 2015, the date of which represented the index date; did not have a concomitant oral anticancer prescription claim on the index date, to isolate the cost-sharing burden associated with the index agent; were not missing OOP cost data for the index agent; had prescription drug coverage through a Medicare Part D prescription drug plan (regardless of low-income subsidy status) or a commercial insurance plan (eg, employer sponsored, retiree, self-purchased); had at least one prescription drug claim and one medical (outpatient or hospital) claim in the 6 months before and after the index date, as a marker for database inclusion during the periods of interest (in keeping with previous studies[8,17,18]); and had no evidence of a paid claim for an oral, injectable, or infusible agent from the same anticancer drug class in the 6 months before the index date, to capture initiation of a new treatment episode. A selection diagram and complete list of included agents are provided in Appendix Figure A1 and Table A1 (online only).

Outcome Measures

Once a claim is adjudicated, it can either be paid (ie, prescription is filled and purchased by the patient) or reversed (ie, the adjudicated prescription is not obtained by the patient and the claim is withdrawn [reversed] by the pharmacy; Appendix Fig A2, online only). First, we classified all patients according to whether they had a reversed claim for their index prescription (yes or no). Next, we classified patients with a reversed claim as having delayed initiation if they had evidence of a purchased prescription for the index agent in the 90 days after their index date and captured time to initiation (in days). Patients with a reversed claim who did not have evidence of a purchased prescription for the index agent in that 90-day period were classified as having abandoned their index agent. Lastly, we assessed whether patients with a reversed claim had evidence of access to any cancer treatment in the 90 days after adjudication of the index prescription,[8,19,20] in the form of a paid claim for any oral anticancer agent from the same drug class or any oral, injectable, or infusible anticancer agent from the same drug class.

Analytic Approach

Descriptive statistics were generated for the main sample. Multivariable logistic regressions were used to estimate risk-adjusted rates of reversal, delayed initiation, and abandonment by five OOP cost categories. Model covariates included sociodemographic characteristics capturing age, sex, region, type of insurance, clinical characteristics including Charlson Comorbidity Index score, and indicators for the specific index agent, and type of pharmacy where the index prescription was processed. We included area-level covariates on race and ethnicity, education level, and mean household income from the three-digit zip code prefix of the patient's residence. We also included indicators for year of the index drug claim to control for any temporal trends.

We examined several subgroups of interest. First, given differences in benefit design, we examined Medicare Part D beneficiaries and commercially insured individuals separately. Second, we separately examined patients whose index prescription was submitted to a mail order pharmacy versus other pharmacy (eg, retail pharmacy). In the context of oral anticancer agents, the mail order category is largely a proxy for specialty pharmacies, which often provide personalized follow-up.[21] Third, we examined the results by sex, because some cancers are sex specific. Fourth, because prognosis and expected benefit are likely to factor into both the speed and likelihood of initiating treatment, we examined subgroups of patients by the US Food and Drug Administration–approved indication for their index oral anticancer agent.

We conducted several sensitivity analyses to test the robustness of our findings. First, we repeated our analyses after redefining all study outcomes using a 180-day (*v* 90-day) follow-up window to identify treatment initiation. Second, to eliminate potential off-label users, we required patients to have a medical claims diagnosis of a cancer for which the index agent was indicated. Third, we tightened our selection criteria by requiring that patients have more frequent (ie, quarterly) prescription fill activity and

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medical activity during the pre- and postindex periods. Fourth, we relaxed our selection criteria by removing the requirement of any prescription drug or medical activity in the pre- and postindex periods. Fifth, we repeated our analyses with an additional covariate on whether the patient resided in a state with or without a chemotherapy parity law (stipulating that cost-sharing costs for oral anticancer treatments cannot exceed those for intravenous chemotherapy for privately insured patients) during the index year.[22] Sixth, we included a covariate for month of index date, because patients filling anticancer prescriptions earlier in the calendar year might have higher costs as a result of deductibles.

Finally, we conducted a simulation to explore how abandonment rates might change in light of ongoing trends (eg, high specialty tier coinsurance levels). Using the regression coefficients from our primary analyses, we predicted abandonment rates for the index prescription in a hypothetical scenario where patients in lower OOP cost categories moved into higher OOP cost categories, while holding their sociodemographic and clinical characteristics constant.

Statistical analyses were performed using SAS 9.4 (SAS Institute, Cary, NC) and STATA/MP 14 (STATA, College Station, TX). The University of Pennsylvania Institutional Review Board deemed the study exempt from informed consent procedures because no data were collected directly from patients.

RESULTS

The main sample included 38,111 patients; 18% abandoned their index oral anticancer agent (n = 6,910; Table 1). Mean age was 68.2 years (standard deviation [SD], 11.4 years), and 58.4% of patients were men. The group of patients who abandoned the index prescription were demographically similar to those who filled it; statistically significant differences tended to be minor (ie, within 1 to 3 percentage points). On average, patients who abandoned the index prescription had higher OOP costs than those who filled it (mean, $1,396.48 [SD, $2,257.67; median, $432.04] *v* $284.00 [SD, $939.42; median, $3.36], $P < .001$).

Risk-adjusted rates of claim reversal for the index prescription increased as OOP cost category increased, as did rates of subsequent delayed filling and abandonment of the index agent (Fig 1). Reversal rates ranged from 13% among patients responsible for ≤ $10 to 67% among patients responsible for > $2000. Among patients in the lowest OOP cost category, only 3% had delayed initiation of their index prescription, compared with 18% of patients in the highest OOP cost category. Mean time to initiation among delayed fillers was 34.8 days (SD, 18.4 days); times were similar across all OOP cost categories (data not shown). Even after accounting for delayed initiation during the 90 days after initial adjudication, risk-adjusted rates of abandonment of the index prescription were significantly higher in the higher OOP cost categories (Fig 1 and Table 2). Whereas only 10% of patients in the lowest OOP cost category abandoned their prescription, almost half of patients (49%) in the highest OOP cost category did. Overall, rates of no fill of any anticancer treatment (ie, no evidence of receiving any oral, injectable, or infusible medication) were quite similar to index agent abandonment rates, suggesting that few patients went on to initiate alternate treatment in the 90 days after the adjudication date for their index prescription (Table 2).

Full regression results for all outcomes are provided in Appendix Table A2 (online only). Of note, patients living in a three-digit zip code area with a higher proportion of high school graduates had lower odds of abandoning anticancer treatment, whereas those living in an area with a higher proportion of black residents had higher odds of treatment abandonment.

In all subgroup analyses, we observed similar associations between OOP cost category and abandonment of the index agent. However, absolute risk-adjusted abandonment rates were generally higher among commercially insured patients (as compared with Medicare Part D beneficiaries) and among other pharmacy customers (as compared with mail order customers; Table 3 and Appendix Table A2). Among selected indications, abandonment rates were lowest for agents indicated for chronic lymphocytic leukemia and highest for agents indicated for metastatic renal cell carcinoma. Even after accounting for the use of available infusible agents in the latter group, rates remained similar (Appendix Table A3, online only).

Table 4 lists predicted rates of abandonment of the index agent under a hypothetical scenario where patients' cost sharing shifted from their current OOP cost category to higher OOP cost categories. If patients responsible for $50.01 to $100 in OOP costs for their index prescription were to be subject to OOP costs of $100.01 to $500, for example, their abandonment rate would be expected to be twice as high, from an observed rate of 16.0% (95% CI, 13.5% to 18.4%) to a predicted rate of 35.9% (95% CI, 32.0% to 39.9%). Abandonment rates for this group would be expected to be 54.0% (95% CI, 48.5% to 59.4%) if OOP costs were to increase to > $2,000. Extensive sensitivity analyses confirmed the robustness of our main results (Appendix Tables A4 and A5, online only).

DISCUSSION

Our analyses demonstrated that higher OOP costs were associated with increased rates of delayed initiation and abandonment of insurer-approved prescriptions for a new course of therapy with a novel oral anticancer agent. Approximately one in eight patients in our sample faced OOP costs > $2,000 for their first prescription, and nearly half of those patients abandoned their approved oral anticancer prescription at the pharmacy. In the current market, OOP costs of this magnitude are typical for most Medicare Part D patients without low-income subsidies[6,23] and for many commercially insured patients, including those enrolled in high-deductible health plans or plans that place these agents on specialty tiers requiring high coinsurance levels.[1,2] Given that we focused on new treatment episodes, our findings suggest that financial barriers may be limiting patients' ability to access what may be the provider's and/or patient's first-choice medication. Regardless of the potential effect on long-term clinical outcomes, such obstacles are likely to exacerbate the perceived or actual financial burden associated with cancer treatment and can inflict emotional distress at a time when patients are already coping with a life-altering diagnosis or change in clinical status.[24-26]

Further, we found that 45% of patients in the highest OOP cost category had no evidence of receiving any oral, injectable, or infusible anticancer agent in the 90 days after their initial claim adjudication date, despite the fact that infusible agents covered under a patient's medical benefit may be available at much lower OOP cost, particularly for Medicare beneficiaries. These patterns were evident across insurance type, pharmacy type, sex, and

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Table 1. Sample Characteristics of Patients with a New Adjudicated Prescription for a Novel Oral Anticancer Agent

Characteristic	Total Patients	Patients Who Filled Index Oral Anticancer Agent*	Patients Who Abandoned Index Oral Anticancer Agent†	*P*
Total No.	38,111	31,201	6,910	
Mean age, years (SD)	68.2 (11.4)	68.3 (11.3)	67.8 (11.6)	.004
Age category, years, No. (%)				< .001
≤ 54	4,437 (11.6)	3,589 (11.5)	848 (12.3)	
55-64	6,884 (18.1)	5,717 (18.3)	1,167 (16.9)	
65-69	6,319 (16.6)	5,034 (16.1)	1,285 (18.6)	
70-74	6,898 (18.1)	5,610 (18.0)	1,288 (18.6)	
75-80	13,573 (35.6)	11,251 (36.1)	2,322 (33.6)	
Sex, No. (%)				.002
Male	22,267 (58.4)	18,346 (58.8)	3,921 (56.7)	
Female	15,844 (41.6)	12,855 (41.2)	2,989 (43.3)	
Sociodemographic variables in patient's area of residence‡				
Race, proportion of residents, mean (SD)				
Black	0.131 (0.127)	0.131 (0.127)	0.131 (0.126)	.92
White	0.755 (0.154)	0.755 (0.154)	0.754 (0.152)	.48
Other	0.114 (0.092)	0.114 (0.092)	0.116 (0.093)	.18
Ethnicity, proportion of Hispanic residents, mean (SD)	0.147 (0.149)	0.145 (0.148)	0.153 (0.157)	< .001
Education, proportion of residents with high school degree or higher, mean (SD)	0.873 (0.049)	0.872 (0.049)	0.870 (0.050)	.006
Mean household income, $ (SD)	74,740 (20,173)	74,764 (20,274)	74,628 (19,709)	.61
Region, No. (%)				.008
Midwest	9,110 (23.9)	7,531 (24.1)	1,579 (22.9)	
Northeast	7,188 (18.9)	5,936 (19.0)	1,252 (18.1)	
South	16,264 (42.7)	13,242 (42.4)	3,022 (43.7)	
West	5,549 (14.6)	4,492 (14.4)	1,057 (15.3)	
Insurance type, No. (%)				< .001
Commercial	13,659 (35.8)	10,895 (34.9)	2,764 (40.0)	
Medicare Part D	24,452 (64.2)	20,306 (65.1)	4,146 (60.0)	
Pharmacy type,§ No. (%)				< .001
Mail order	24,776 (65.0)	21,456 (68.8)	3,320 (48.0)	
Other	13,335 (35.0)	9,745 (31.2)	3,590 (52.0)	
Mean Charlson Comorbidity Index score (SD)	0.50 (1.02)	0.49 (1.01)	0.57 (1.11)	< .001
Index year, No. (%)				< .001
2014	16,037 (42.1)	12,524 (40.1)	3,513 (50.8)	
2015	22,074 (57.9)	18,677 (59.9)	3,397 (49.2)	
Mean out-of-pocket payment, $ (SD)	485.71 (1,352.87)	284.00 (939.42)	1,396.48 (2,257.67)	< .001
Out-of-pocket payment category, No. (%)				< .001
≤ $10	21,990 (57.7)	19,974 (64.0)	2,016 (29.2)	
$10.01-$50	5,975 (15.7)	5,302 (17.0)	673 (9.7)	
$50.01-$100	1,665 (4.4)	1,399 (4.5)	266 (3.8)	
$100.01-$500	1,888 (5.0)	1,196 (3.8)	692 (10.0)	
$500.01-$2,000	1,828 (4.8)	927 (3.0)	901 (13.0)	
> $2,000	4,765 (12.5)	2,403 (7.7)	2,362 (34.2)	

Abbreviation: SD, standard deviation.
*Patient paid for (filled) the approved index oral anticancer prescription upon approval or after a delay.
†Patient had no evidence of a prescription fill for the index oral anticancer agent within 90 days of the index prescription date.
‡Area-level variables were calculated at the three-digit zip code level for the patient's residence. Education variable was captured based on residents ≥ 25 years of age.
§In the case of oral anticancer agents, mail order is largely a proxy for specialty pharmacies. Other category includes retail pharmacies.

indication even when controlling for relevant patient and clinical characteristics. Abandonment rates decreased only slightly (3% to 4%) when we extended our follow-up window to 180 days. Further, our simulation showed that if high OOP cost is indeed a causal factor, abandonment rates for patients in lower OOP cost groups are likely to double with relatively modest increases in patients' OOP cost obligations, which is a likely scenario given ongoing marketplace trends.

The abandonment rates we found for oral anticancer agents were much higher than those previously reported by Streeter et al[8] in 2011, possibly because their study used data from 2007 to 2009 and only 1.4% of sampled patients faced OOP costs > $500. Indeed, our observed rates were more consistent with analyses of more recent prescription abandonment data for specialty drugs for multiple sclerosis and rheumatoid arthritis.[19] This is surprising given that patients are likely to perceive cancer as more immediately life threatening. In addition, although the highest abandonment rates were observed for drugs indicated for advanced cancers where prognosis may influence treatment initiation decisions, abandonment rates were also substantial among patients treated for chronic myeloid leukemia (≥ 35% with cost sharing > $500), where oral anticancer therapy is life saving and has the potential to transform the condition into a chronic disease.[27,28]

Our findings point to the importance of patient-provider conversations that address both financial and clinical implications

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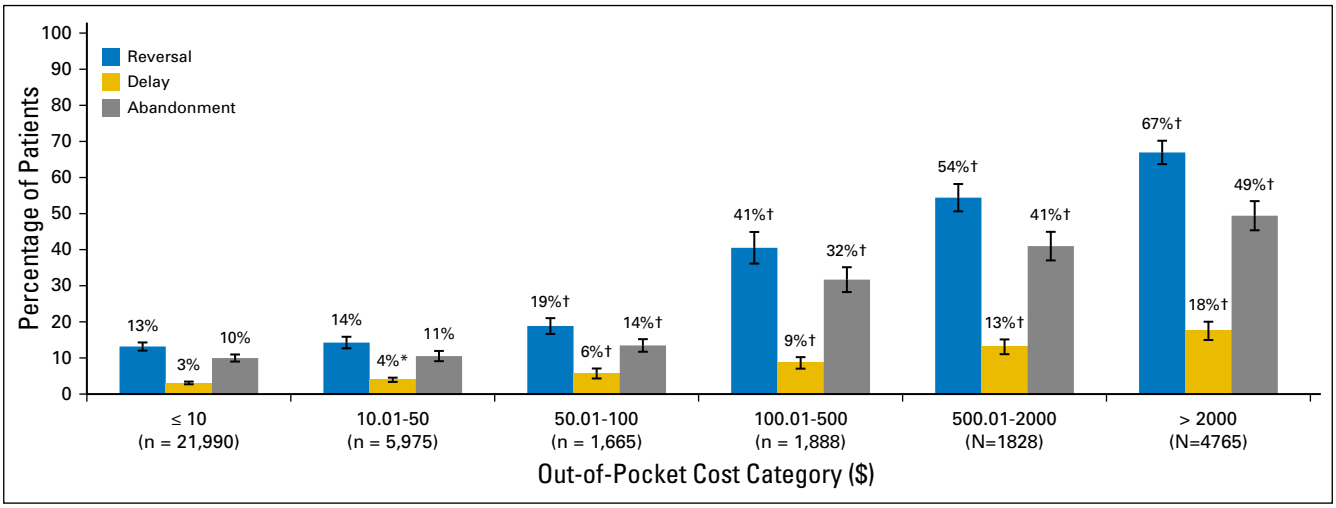

Fig 1. Risk-adjusted rates of patient reversal, delay, and abandonment of new index oral anticancer prescription. Reversal indicates that the patient's insurance company approved the prescription but the patient did not fill it (ie, purchase it from the pharmacy) and the claim was withdrawn by the pharmacy. Delay indicates that the patient filled (purchased) a prescription for the index oral anticancer agent within 90 days of the index prescription date. Abandonment indicates that the patient had no evidence of a prescription fill for the index oral anticancer agent within 90 days of the index prescription date. (*) $P < .05$ compared to ≤ $10 out-of-pocket cost category. (†) $P < .01$ compared to ≤ $10 out-of-pocket cost category.

of treatment to allow for evaluation of any alternate, lower OOP cost treatment options in a timely fashion.[29] This is especially important with self-administered treatments, where initiation delay and nonadherence are more difficult to monitor; unlike missed visits for hospital- or office-based treatments, clinicians may be unaware that a patient has opted not to fill (or refill) an oral prescription. Our data also suggest that it may be particularly important to address financial barriers with patients who have multiple risk factors for health disparities; our available area-level data were imprecise, but we still found that individuals residing in an area with lower education level and in an area with a higher proportion of black residents had lower odds of accessing treatment.

Multiple factors are contributing to high OOP costs for cancer patients, including the increase in high-deductible health plans, growing use of specialty tiers with coinsurance, high drug prices, and greater availability of (and demand for) specialty drugs across conditions. Hence, there are likely multiple avenues to reducing financial burden on patients. Our results highlight the pressing need for all stakeholders, including manufacturers, pharmacy benefit managers, payers, and policymakers, to identify fiscally sustainable strategies to improve patient access to cancer medications.

Our study has limitations. First, our cross-sectional design revealed consistent associations but did not permit us to assess causality. Second, electronic prescribing has become extremely common, but our time-to-initiation measure may have underestimated delays in cases where patients received a paper prescription and did not immediately bring it to the pharmacy. Third, we interpret our results in the context of the strengths and limitations of our data source. The database allowed us to examine patients who were enrolled in a wide range of insurance plans and facing varying cost-sharing levels, and it included data specific to adjudication, prescription claim reversal, and true OOP costs. However, it may not have captured all pharmacies or facilities where patients received treatment, potentially leading us to erroneously classify some patients as not initiating or delaying treatment and to correspondingly underestimate overall initiation rates. Nonetheless, we applied sample selection criteria to maximize our ability to detect any subsequent anticancer treatment initiation

Table 2. Risk-Adjusted Rates in Overall Sample of Patients With a New Adjudicated Prescription for a Novel Oral Anticancer Agent

Outcome	Risk-Adjusted Rates (% [95% CI]) by Out-of-Pocket Cost Category					
	≤ $10 (n = 21,990)	$10.01-$50 (n = 5,975)	$50.01-$100 (n = 1,665)	$100.01-$500 (n = 1,888)	$500.01-$2,000 (n = 1,828)	> $2,000 (n = 4,765)
Abandonment of index oral anticancer prescription*	10.0 (9.0 to 11.0)	10.5 (9.1 to 12.0)	13.5† (11.7 to 15.2)	31.7† (28.3 to 35.1)	41.0† (37.0 to 44.9)	49.4† (45.4 to 53.4)
No fill of any oral anticancer agent‡	9.8 (8.8 to 10.8)	10.3 (8.9 to 11.7)	12.9† (11.2 to 14.6)	30.9† (27.3 to 34.4)	39.9† (36.0 to 43.7)	48.0† (43.8 to 52.1)
No fill of any oral, injectable, or infusible anticancer agent§	9.4 (8.5 to 10.4)	9.9 (8.5 to 11.3)	12.5† (10.8 to 14.3)	29.2† (25.6 to 32.8)	38.2† (34.3 to 42.0)	45.4† (41.2 to 49.5)

*Patient had no evidence of a prescription fill for the index oral anticancer agent within 90 days of the index prescription date.
†$P < .01$ compared with ≤ $10 out-of-pocket cost category.
‡Patient had no evidence of a prescription fill for any oral anticancer agent within 90 days of the index prescription date.
§Patient had no evidence of a claim for any oral, injectable, or infusible anticancer agent within 90 days of the index prescription date.

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Table 3. Risk-Adjusted Index Oral Anticancer Prescription Abandonment Rates* for Subgroups by Insurance Type, Pharmacy Type, Sex, and Indication

Subgroup	No. of Patients	Abandonment Rate (% [95% CI]) by Out-of-Pocket Cost Category					
		≤ $10	$10.01-$50	$50.01-$100	$100.01-$500	$500.01-$2,000	> $2,000
Insurance type							
Commercial	13,659	13.7 (12.2 to 15.2)	13.5 (12.1 to 15.0)	17.1† (13.8 to 20.3)	29.1† (25.1 to 33.2)	44.2† (33.7 to 54.8)	66.9† (57.5 to 76.2)
Medicare Part D	24,452	8.1 (7.0 to 9.1)	10.1 (7.6 to 12.5)	12.2† (9.4 to 15.1)	33.2† (28.9 to 37.4)	37.7† (34.6 to 40.8)	42.1† (40.4 to 43.9)
Pharmacy type‡							
Mail order	24,776	6.1 (5.3 to 7.0)	7.0 (5.5 to 8.4)	11.1† (8.5 to 13.7)	28.4† (23.2 to 33.5)	35.6† (31.2 to 40.1)	46.7† (42.7 to 50.7)
Other	13,335	17.9 (16.2 to 19.5)	17.3 (14.8 to 19.7)	17.5 (14.9 to 20.0)	38.8† (34.0 to 43.5)	51.0† (45.3 to 56.7)	55.6† (50.2 to 61.0)
Sex							
Male	22,267	9.3 (8.3 to 10.3)	9.8 (8.2 to 11.3)	12.2† (10.2 to 14.2)	30.0† (26.6 to 33.3)	41.4† (37.2 to 45.6)	48.1† (43.6 to 52.6)
Female	15,844	11.0 (9.8 to 12.2)	11.6 (9.9 to 13.3)	14.8† (11.8 to 17.8)	33.7† (29.0 to 38.5)	40.1† (35.2 to 45.0)	50.6 † (46.5 to 54.8)
Selected indications§							
Chronic lymphocytic leukemia	4,773	3.6 (3.0 to 4.3)	4.7 (3.3 to 6.2)	8.4† (3.5 to 13.3)	18.5† (11.8 to 25.2)	28.5† (21.1 to 35.9)	36.0† (31.1 to 40.9)
Chronic myeloid leukemia	3,893	8.0 (6.6 to 9.3)	7.5 (5.2 to 9.8)	9.3 (5.7 to 12.9)	24.2† (18.1 to 30.3)	34.8† (27.6 to 42.1)	41.4† (33.3 to 49.6)
Multiple myeloma	8,195	6.5 (5.0 to 7.9)	8.0 (5.7 to 10.3)	13.4† (8.6 to 18.1)	37.2† (27.7 to 46.8)	41.2† (34.2 to 48.1)	45.2† (39.2 to 51.2)
Metastatic prostate cancer	5,717	7.1 (5.9 to 8.4)	7.8 (4.9 to 10.7)	9.4 (5.2 to 13.7)	28.2† (22.1 to 34.3)	39.9† (31.1 to 48.8)	38.3† (32.8 to 43.7)
Metastatic renal cell carcinoma	4,683	15.2 (12.8 to 17.6)	11.5 (8.2 to 14.8)	16.9 (11.7 to 22.0)	28.3† (22.9 to 33.8)	46.2† (39.4 to 53.1)	63.9† (58.9 to 68.9)

*Patient had no evidence of a prescription fill for the index oral anticancer agent within 90 days of the index prescription date.
†$P < .01$ compared with ≤ $10 out-of-pocket cost category.
‡In the case of oral anticancer agents, mail order is largely a proxy for specialty pharmacies. Other category includes retail pharmacies.
§Patients were classified according to US Food and Drug Administration–approved indication for the index oral anticancer agent. The top five indications based on sample size, representing 70% of the overall study sample, are presented. Chronic lymphocytic leukemia agents included ibrutinib and idelalisib. Chronic myeloid leukemia agents included bosutinib, dasatinib, imatinib, nilotinib, omacetaxine, and ponatinib. Multiple myeloma agents included lenalidomide, pomalidomide, and thalidomide. Metastatic prostate cancer agents included abiraterone, enzalutamide, and nilutamide. Metastatic renal cell carcinoma agents included axitinib, pazopanib, sorafenib, and sunitinib. Everolimus was excluded from the subgroup analysis for metastatic renal cell carcinoma because it was also approved for other cancers.

during our follow-up period, and sensitivity analyses with varied selection criteria did not suggest systematic differences in data capture across OOP cost categories. As with traditional insurance claims data sets, we also could not detect cases where patients obtained free medication through manufacturer programs or other means. However, this is unlikely to explain the high rates of abandonment we observed, and workaround strategies may still involve considerable stress and effort for the patient and family. We were unable to identify cases where treatment may have been abandoned in favor of hospice or the degree to which financial barriers may have figured into those decisions. Finally, our study focused specifically on obstacles at initiation and did not have the clinical detail or mortality data required to assess longer-term effect on health outcomes and survival.

In conclusion, as the availability of oral anticancer treatment options continues to increase, access and affordability will determine the true benefit for patients. Ongoing, methodologically rigorous research will be needed to evaluate the effect of OOP costs and to identify sustainable strategies that encourage prompt access and appropriate adherence to oral anticancer medications.

Table 4. Predicted Risk-Adjusted Abandonment Rates if Out-of-Pocket Costs Were to Increase to Specified Levels

Out-of-Pocket Cost Category	No. of Patients	Predicted Abandonment Rate (% [95% CI]) by Hypothetical Out-of-Pocket Cost Category					
		≤ $10	$10.01-$50	$50.01-$100	$100.01-$500	$500.01-$2,000	> $2,000
≤ $10	21,990	*9.2 (8.3 to 10.0)*	9.7 (8.2 to 11.1)	12.4 (10.9 to 14.0)	29.8 (26.4 to 33.1)	38.9 (35.2 to 42.5)	47.2 (43.6 to 50.8)
$10.01-$50	5,975		*11.3 (10.1 to 12.4)*	14.4 (11.9 to 17.0)	33.8 (29.5 to 38.1)	43.5 (37.8 to 49.2)	52.1 (45.9 to 58.2)
$50.01-$100	1,665			*16.0 (13.5 to 18.4)*	35.9 (32.0 to 39.9)	45.5 (40.4 to 50.7)	54.0 (48.5 to 59.4)
$100.01-$500	1,888				*36.7 (33.1 to 40.2)*	45.9 (42.1 to 49.7)	54.0 (50.3 to 57.8)
$500.01-$2,000	1,828					*49.3 (45.7 to 52.9)*	57.4 (54.0 to 60.9)
> $2,000	4,765						*49.6 (45.9 to 53.2)*

NOTE. Abandonment indicates patient had no evidence of a prescription fill for the index oral anticancer agent within 90 days of the index prescription date. Predicted abandonment rates use the regression coefficients from our primary analyses to illustrate how abandonment rates for the index oral anticancer prescription might change if patients in the lower out-of-pocket cost categories were to move into higher out-of-pocket cost categories, while holding all their sociodemographic and clinical characteristics constant. Italicized numbers represent observed rates for that out-of-pocket cost subgroup, provided for comparison purposes. For example, if patients responsible for $50.01 to $100 in out-of-pocket costs for their index prescription were to be subject to out-of-pocket costs of $100.01 to $500, their abandonment rate would be expected to be twice as high, from an observed rate of 16.0% (95% CI, 13.5% to 18.4%) to a predicted rate of 35.9% (95% CI, 32.0% to 39.9%).

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Association of Patient Out-of-Pocket Costs With Prescription Abandonment and Delay in Fills of Novel Oral Anticancer Agents

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Appendix

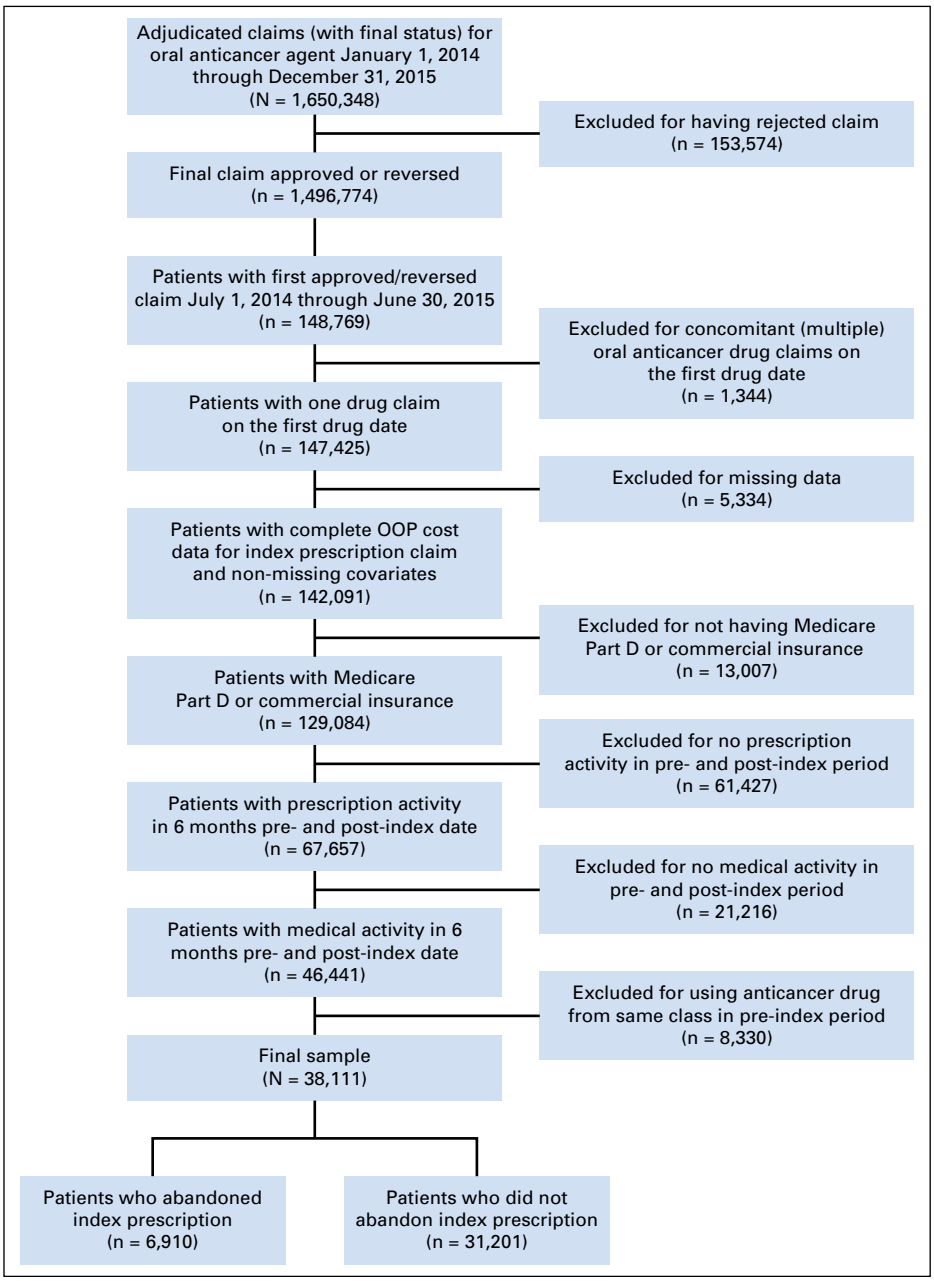

Fig A1. Sample selection diagram. OOP, out of pocket.

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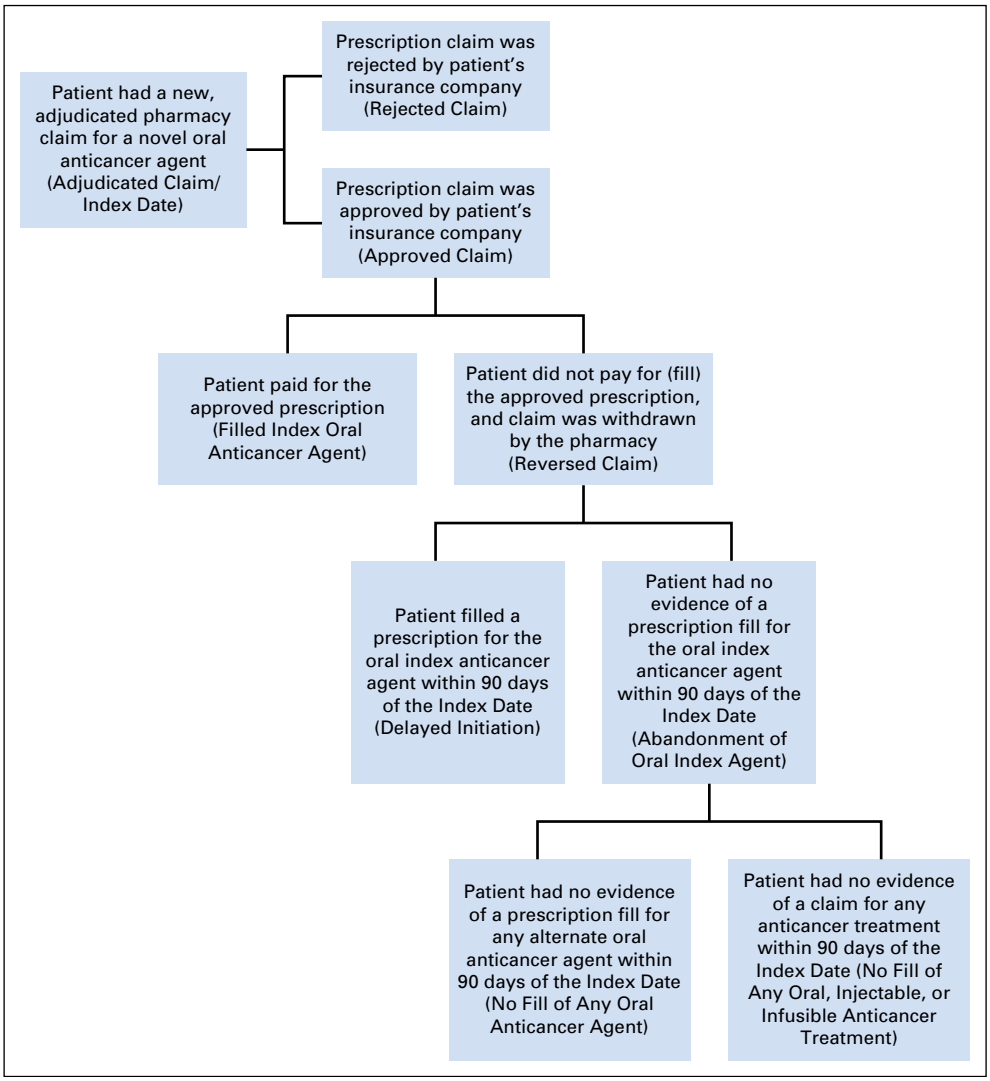

Fig A2. Prescription outcomes infographic.

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Table A1. Full List of Novel Oral Anticancer Agents Included in the Study

Generic (Brand) Drug Name	Final No. of Patients*
Abiraterone (Zytiga)	3,256
Afatinib (Gilotrif)	106
Axitinib (Inlyta)	298
Bexarotene (Targretin)	310
Bosutinib (Bosulif)	95
Cabozantinib (Cometriq)	165
Capecitabine (Xeloda)	1,618
Ceritinib (Zykadia)	50
Crizotinib (Xalkori)	244
Dabrafenib (Tafinlar)	111
Dasatinib (Sprycel)	770
Enzalutamide (Xtandi)	2,287
Erlotinib (Tarceva)	2,621
Everolimus (Afinitor)	2,206
Ibrutinib (Imbruvica)	4,264
Idelalisib (Zydelig)	509
Imatinib (Gleevec)	2,395
Lapatinib (Tykerb)	250
Lenalidomide (Revlimid)	6,925
Nilotinib (Tasigna)	489
Nilutamide (Nilandron)	174
Omacetaxine (Synribo)	6
Pazopanib (Votrient)	1,620
Pomalidomide (Pomalyst)	808
Ponatinib (Iclusig)	138
Regorafenib (Stivarga)	434
Ruxolitinib (Jakafi)	958
Sorafenib (Nexavar)	1,375
Sunitinib (Sutent)	1,390
Temozolomide (Temodar)	593
Thalidomide (Thalomid)	462
Topotecan capsules (Hycamtin)	88
Toremifene (Fareston)	302
Trametinib (Mekinist)	137
Vandetanib (Caprelsa)	86
Vemurafenib (Zelboraf)	146
Vismodegib (Erivedge)	334
Vorinostat (Zolinza)	91

*Number of patients taking the drug who were included after application of all study eligibility criteria. Palbociclib (Ibrance) was eligible for inclusion, but all patients taking this agent were excluded during application of subsequent eligibility criteria.

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Table A2. Full Regression Results: Adjusted Odds Ratios for Main Sample

Characteristic	Odds Ratio (95% CI)				
	Reversed Claim for Index Oral Anticancer Agent[a]	Delayed Fill of Index Oral Anticancer Agent[b]	Abandonment of Index Oral Anticancer Prescription[c]	No Fill of Any Oral Anticancer Agent[d]	No Fill of Any Oral, Injectable, or Infusible Anticancer Agent[e]
OOP cost category					
≤ $10	Reference	Reference	Reference	Reference	Reference
$10.01-$50	1.11 (0.93 to 1.32)	1.30[f] (1.05 to 1.60)	1.07 (0.87 to 1.31)	1.06 (0.86 to 1.32)	1.06 (0.86 to 1.32)
$50.01-$100	1.58[g] (1.35 to 1.85)	1.91[g] (1.45 to 2.50)	1.45[g] (1.22 to 1.71)	1.41[g] (1.19 to 1.67)	1.41[g] (1.18 to 1.68)
$100.01-$500	5.09[g] (3.95 to 6.55)	2.99[g] (2.31 to 3.86)	4.87[g] (3.84 to 6.18)	4.80[g] (3.75 to 6.14)	4.56[g] (3.53 to 5.89)
$500.01-$2,000	9.34[g] (7.90 to 11.05)	4.78[g] (3.92 to 5.82)	7.64[g] (6.33 to 9.23)	7.49[g] (6.23 to 8.99)	7.16[g] (5.94 to 8.64)
> $2,000	16.49[g] (13.62 to 19.96)	6.76[g] (5.40 to 8.47)	11.16[g] (9.27 to 13.44)	10.82[g] (8.97 to 13.06)	9.97[g] (8.25 to 12.06)
Age group, years					
≤ 54	Reference	Reference	Reference	Reference	Reference
55-64	0.95 (0.85 to 1.07)	0.90 (0.75 to 1.08)	0.97 (0.84 to 1.13)	0.97 (0.84 to 1.13)	0.97 (0.84 to 1.12)
65-69	1.08 (0.93 to 1.26)	0.80 (0.63 to 1.02)	1.17 (0.98 to 1.39)	1.17 (0.98 to 1.40)	1.16 (0.96 to 1.39)
70-74	0.98 (0.81 to 1.18)	0.75[f] (0.57 to 0.99)	1.07 (0.88 to 1.30)	1.08 (0.89 to 1.32)	1.10 (0.89 to 1.35)
75-80	0.98 (0.81 to 1.18)	0.77 (0.59 to 1.00)	1.06 (0.87 to 1.31)	1.08 (0.88 to 1.34)	1.11 (0.89 to 1.37)
Sex					
Male	Reference	Reference	Reference	Reference	Reference
Female	1.09[g] (1.02 to 1.16)	1.16[f] (1.06 to 1.28)	1.03 (0.96 to 1.11)	1.03 (0.96 to 1.10)	1.04 (0.96 to 1.11)
Charlson Comorbidity Index score	1.11[g] (1.08 to 1.15)	1.04 (0.99 to 1.08)	1.12[g] (1.08 to 1.15)	1.12[g] (1.08 to 1.15)	1.12[g] (1.08 to 1.15)
Insurance type					
Commercial	Reference	Reference	Reference	Reference	Reference
Medicare Part D	0.70[g] (0.55 to 0.90)	1.02 (0.75 to 1.40)	0.66[f] (0.48 to 0.91)	0.66[f] (0.48 to 0.91)	0.68[f] (0.49 to 0.95)
Pharmacy type[h]					
Other	Reference	Reference	Reference	Reference	Reference
Mail order	0.56[g] (0.50 to 0.63)	0.83[g] (0.74 to 0.94)	0.56[g] (0.49 to 0.64)	0.55[g] (0.48 to 0.63)	0.54[g] (0.47 to 0.61)
Region					
Midwest	Reference	Reference	Reference	Reference	Reference
Northeast	1.10 (0.97 to 1.26)	1.15 (0.99 to 1.33)	1.06 (0.92 to 1.22)	1.05 (0.92 to 1.21)	1.02 (0.90 to 1.17)
South	0.98 (0.88 to 1.08)	1.07 (0.93 to 1.23)	0.95 (0.83 to 1.07)	0.96 (0.85 to 1.09)	0.94 (0.83 to 1.07)
West	1.14 (0.99 to 1.30)	1.07 (0.89 to 1.29)	1.13 (0.97 to 1.31)	1.13 (0.97 to 1.31)	1.13 (0.97 to 1.31)
Area-level sociodemographic variables[i]					
Race, proportion of residents					
White	Reference	Reference	Reference	Reference	Reference
Black	1.03[f] (1.00 to 1.07)	1.01 (0.97 to 1.06)	1.04[f] (1.00 to 1.07)	1.04[f] (1.00 to 1.07)	1.04[f] (1.01 to 1.08)
Other	0.99 (0.94 to 1.04)	1.02 (0.95 to 1.10)	0.98 (0.93 to 1.03)	0.98 (0.93 to 1.04)	0.98 (0.93 to 1.03)
Ethnicity, proportion of residents					
Non-Hispanic	Reference	Reference	Reference	Reference	Reference
Hispanic	1.01 (0.98 to 1.03)	1.02 (0.97 to 1.07)	1.00 (0.97 to 1.03)	1.00 (0.97 to 1.03)	1.00 (0.97 to 1.03)
Education, proportion of residents with high school degree or higher	0.94 (0.85 to 1.04)	1.13 (0.94 to 1.36)	0.88[f] (0.78 to 1.00)	0.87[f] (0.78 to 0.98)	0.88[f] (0.78 to 0.99)
Income, mean household ($10,000s)	0.99 (0.96 to 1.01)	0.99 (0.95 to 1.02)	0.99 (0.97 to 1.02)	1.00 (0.97 to 1.02)	1.00 (0.97 to 1.02)
Test for overall model					
Wald χ^2	4,109.36[g]	1,433.18[g]	3,599.99[g]	3,579.95[g]	3,231.15[g]
Joint test for OOP variables					
Wald χ^2	1,091.94[g]	351.64[g]	859.74[g]	861.07[g]	775.98[g]

NOTE. Estimates for the 38 indicators for the index oral anticancer agents are not shown.
Abbreviation: OOP, out of pocket.
[a]Patient's insurance company approved the prescription, but the patient did not fill it (ie, purchase it from the pharmacy), and the claim was withdrawn by the pharmacy.
[b]Patient filled (purchased) the index oral anticancer agent within 90 days of the index prescription date.
[c]Patient had no evidence of a prescription fill for the index oral anticancer agent within 90 days of the index prescription date.
[d]Patient had no evidence of a prescription fill for any oral anticancer agent within 90 days of the index prescription date.
[e]Patient had no evidence of a claim for any oral, injectable, or infusible anticancer agent within 90 days of the index prescription date.
[f]$P < .05$.
[g]$P < .01$.
[h]In the case of oral anticancer agents, mail order is largely a proxy for specialty pharmacies. Other category includes retail pharmacies.
[i]Area-level variables were calculated at the three-digit zip code level for the patient's residence. Education variable was captured based on residents ≥ 25 years old. For race, ethnicity, and education, odds ratios indicate that for every 10% increase in the proportion of residents in the specified category, odds of the outcome change by the ratio presented. For example, for every 10% increase in the proportion of black residents in the patient's area of residence, there is an associated 4% increase in the odds of claim reversal. For income, odds ratios indicate that for every $10,000 increase in the mean area-level household income, odds of the outcome change by the ratio presented.

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Table A3. Risk-Adjusted Rates for Subgroups by Insurance Type, Pharmacy Type, Sex, and Selected Indications

Subgroup	Risk-Adjusted Rates (% [95% CI]) by Out-of-Pocket Cost Category					
	≤ $10	$10.01-$50	$50.01-$100	$100.01-$500	$500.01-$2,000	> $2,000
Insurance type						
Commercial						
No. of patients	6,152	4,263	1,058	664	492	1,030
Reversal of index oral prescription	17.3 (15.8 to 18.9)	17.3 (15.8 to 18.9)	23.3* (19.6 to 26.9)	37.8* (32.6 to 43.0)	62.3* (52.9 to 71.6)	82.5* (76.6 to 88.4)
Delayed fill of index oral anticancer agent	3.6 (2.9 to 4.3)	3.9 (3.2 to 4.5)	6.4* (4.5 to 8.2)	8.6* (6.1 to 11.1)	17.7* (12.7 to 22.7)	14.0* (8.2 to 19.8)
Abandonment of index oral prescription	13.7 (12.2 to 15.2)	13.5 (12.1 to 15.0)	17.1* (13.8 to 20.3)	29.1* (25.1 to 33.2)	44.2* (33.7 to 54.8)	66.9* (57.5 to 76.2)
No fill of any oral anticancer agent	13.5 (12.0 to 15.0)	13.3 (11.9 to 14.7)	16.5† (13.3 to 19.7)	28.3* (24.6 to 32.0)	42.7* (32.4 to 53.1)	65.6* (55.8 to 75.4)
No fill of any oral, injected, or infusible anticancer agent	12.7 (11.3 to 14.2)	12.5 (11.2 to 13.9)	15.9* (12.5 to 19.2)	26.5* (22.8 to 30.2)	40.5* (30.2 to 50.9)	61.4* (51.4 to 71.5)
Medicare Part D						
No. of patients	15,838	1,712	607	1,224	1,336	3,735
Reversal of index oral prescription	11.0 (9.7 to 12.2)	14.6* (11.9 to 17.3)	17.4* (13.8 to 21.0)	42.1* (36.8 to 47.5)	49.9* (46.3 to 53.4)	60.8* (58.1 to 63.4)
Delayed fill of index oral anticancer agent	2.9 (2.4 to 3.3)	4.4* (3.5 to 5.4)	5.2* (2.9 to 7.5)	8.9* (6.9 to 10.8)	11.8* (9.9 to 13.7)	18.5* (16.5 to 20.5)
Abandonment of index oral prescription	8.1 (7.0 to 9.1)	10.1 (7.6 to 12.5)	12.2* (9.4 to 15.1)	33.2* (28.9 to 37.4)	37.7* (34.6 to 40.8)	42.1* (40.4 to 43.9)
No fill of any oral anticancer agent	7.9 (6.9 to 8.9)	9.9 (7.5 to 12.3)	11.7* (9.0 to 14.5)	32.4* (27.9 to 36.8)	36.7* (33.7 to 39.6)	40.6* (38.9 to 42.3)
No fill of any oral, injected, or infusible anticancer agent	7.7 (6.7 to 8.7)	9.6 (7.3 to 11.9)	11.1† (8.4 to 13.7)	30.9* (26.5 to 35.3)	35.3* (32.6 to 38.1)	38.6* (36.8 to 40.4)
Pharmacy type‡						
Mail order						
No. of patients	15,334	3,636	995	1,099	989	2,723
Reversal of index oral prescription	9.0 (7.9 to 10.0)	9.9 (8.3 to 11.6)	16.6* (13.3 to 19.9)	36.7* (30.1 to 43.2)	48.5* (44.1 to 53.0)	65.4* (62.1 to 68.7)
Delayed fill of index oral anticancer agent	2.7 (2.4 to 3.1)	3.1 (2.5 to 3.8)	5.7* (3.9 to 7.5)	8.0* (5.9 to 10.2)	12.4* (10.1 to 14.8)	18.8* (15.9 to 21.8)
Abandonment of index oral prescription	6.1 (5.3 to 7.0)	7.0 (5.5 to 8.4)	11.1* (8.5 to 13.7)	28.4* (23.2 to 33.5)	35.6* (31.2 to 40.1)	46.7* (42.7 to 50.7)
No fill of any oral anticancer agent	5.9 (5.2 to 6.7)	6.7 (5.3 to 8.1)	10.4* (7.9 to 12.9)	27.3* (22.1 to 32.6)	34.4* (30.1 to 38.8)	45.0* (41.0 to 49.1)
No fill of any oral, injected, or infusible anticancer agent	5.6 (4.8 to 6.4)	6.3 (4.9 to 7.6)	10.1* (7.6 to 12.5)	25.5* (20.2 to 30.7)	32.6* (28.3 to 36.8)	42.3* (38.3 to 46.3)
Other						
No. of patients	6,656	2,339	670	789	839	2,042
Reversal of index oral prescription	21.7 (19.8 to 23.6)	22.5 (19.6 to 25.3)	23.0 (20.1 to 25.8)	48.4* (43.6 to 53.3)	64.7* (59.6 to 69.8)	71.2* (67.2 to 75.3)
Delayed fill of index oral anticancer agent	3.8 (3.2 to 4.4)	5.4† (4.3 to 6.4)	5.7† (4.0 to 7.4)	9.8* (7.5 to 12.0)	14.0* (11.2 to 16.8)	16.0* (13.5 to 18.4)
Abandonment of index oral prescription	17.9 (16.2 to 19.5)	17.3 (14.8 to 19.7)	17.5 (14.9 to 20.0)	38.8* (34.0 to 43.5)	51.0* (45.3 to 56.7)	55.6* (50.2 to 61.0)
No fill of any oral anticancer agent	17.7 (16.0 to 19.3)	17.1 (14.7 to 19.6)	17.2 (14.7 to 19.7)	38.2* (33.5 to 42.9)	50.0* (44.4 to 55.6)	54.4* (48.8 to 59.9)
No fill of any oral, injected, or infusible anticancer agent	17.2 (15.5 to 18.8)	16.8 (14.3 to 19.2)	16.6 (14.0 to 19.3)	36.7* (32.1 to 41.3)	48.5* (42.8 to 54.2)	52.1* (46.5 to 57.6)
Sex						
Male						
No. of patients	12,740	3,477	941	1,125	1,033	2,951
Reversal of index oral prescription	12.2 (11.1 to 13.4)	13.5 (11.7 to 15.2)	17.4* (15.0 to 19.8)	38.5* (34.1 to 42.9)	54.5* (50.4 to 58.6)	65.2* (61.5 to 68.9)
Delayed fill of index oral anticancer agent	2.9 (2.5 to 3.2)	3.9† (3.1 to 4.6)	5.4* (3.9 to 6.9)	8.3* (6.2 to 10.5)	12.7* (9.9 to 15.4)	16.9* (14.3 to 19.5)
Abandonment of index oral prescription	9.3 (8.3 to 10.3)	9.8 (8.2 to 11.3)	12.2* (10.2 to 14.2)	30.0* (26.6 to 33.3)	41.4* (37.2 to 45.6)	48.1* (43.6 to 52.6)
No fill of any oral anticancer agent	9.0 (8.0 to 10.0)	9.5 (8.0 to 11.0)	11.9* (10.0 to 13.8)	29.0* (25.5 to 32.6)	40.2* (36.0 to 44.3)	46.5* (41.8 to 51.2)
No fill of any oral, injected, or infusible anticancer agent	8.7 (7.7 to 9.6)	9.0 (7.6 to 10.5)	11.4* (9.4 to 13.3)	27.6* (24.1 to 31.1)	38.5* (34.4 to 42.6)	44.1* (39.4 to 48.9)
Female						
No. of patients	9,250	2,498	724	763	795	1,814
Reversal of index oral prescription	14.5 (13.1 to 15.9)	15.4 (13.4 to 17.4)	20.5* (17.0 to 24.0)	43.1* (37.7 to 48.4)	54.2* (49.4 to 59.1)	69.1* (65.8 to 72.4)
Delayed fill of index oral anticancer agent	3.4 (2.9 to 3.9)	4.1 (3.3 to 4.9)	6.1* (3.9 to 8.3)	9.1* (6.8 to 11.5)	14.1* (11.3 to 16.9)	18.6* (15.6 to 21.6)
Abandonment of index oral prescription	11.0 (9.8 to 12.2)	11.6 (9.9 to 13.3)	14.8* (11.8 to 17.8)	33.7* (29.0 to 38.5)	40.1* (35.2 to 45.0)	50.6* (46.5 to 54.8)
No fill of any oral anticancer agent	10.9 (9.7 to 12.1)	11.4 (9.7 to 13.2)	14.0* (11.2 to 16.8)	33.1* (28.3 to 37.8)	39.1* (34.5 to 43.8)	49.3* (45.1 to 53.5)
No fill of any oral, injected, or infusible anticancer agent	10.5 (9.3 to 11.6)	11.1 (9.5 to 12.8)	13.7* (10.9 to 16.4)	31.1* (26.5 to 35.8)	37.5* (32.8 to 42.1)	46.4* (42.2 to 50.5)

(continued on following page)

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Table A3. Risk-Adjusted Rates for Subgroups by Insurance Type, Pharmacy Type, Sex, and Selected Indications (continued)

Subgroup	Risk-Adjusted Rates (% [95% CI]) by Out-of-Pocket Cost Category					
	≤ $10	$10.01-$50	$50.01-$100	$100.01-$500	$500.01-$2,000	> $2,000
Selected indications§						
Chronic lymphocytic leukemia						
No. of patients	3,211	715	129	162	114	442
Reversal of index oral prescription	6.3 (5.3 to 7.3)	9.6* (7.6 to 11.6)	13.1* (7.8 to 18.4)	27.3* (19.7 to 34.9)	47.8* (39.5 to 56.1)	60.0* (55.0 to 65.0)
Delayed fill of index oral anticancer agent	2.6 (2.0 to 3.3)	5.1* (3.6 to 6.5)	4.8 (1.2 to 8.4)	8.5* (4.1 to 12.8)	19.7* (11.8 to 27.6)	24.8* (20.3 to 29.2)
Abandonment of index oral prescription	3.6 (3.0 to 4.3)	4.7 (3.3 to 6.2)	8.4* (3.5 to 13.3)	18.5* (11.8 to 25.2)	28.5* (21.1 to 35.9)	36.0* (31.1 to 40.9)
No fill of any oral anticancer agent	3.5 (2.9 to 4.1)	4.6 (3.2 to 5.9)	8.2† (3.4 to 13.1)	16.8* (10.6 to 23.1)	27.9* (20.3 to 35.6)	34.8* (29.8 to 39.8)
No fill of any oral, injected, or infusible anticancer agent	3.2 (2.5 to 3.9)	4.2 (2.9 to 5.5)	6.9† (2.4 to 11.4)	16.0* (9.9 to 22.1)	25.8* (18.7 to 32.9)	30.2* (25.7 to 34.7)
Chronic myeloid leukemia						
No. of patients	2,018	728	244	238	188	477
Reversal of index oral prescription	11.1 (9.6 to 12.7)	11.7 (8.8 to 14.7)	15.9† (11.6 to 20.1)	34.5* (28.3 to 40.7)	50.5* (43.0 to 57.9)	65.9* (59.5 to 72.3)
Delayed fill of index oral anticancer agent	3.2 (2.4 to 4.1)	4.4 (2.4 to 6.3)	6.5† (3.0 to 10.1)	10.3* (6.5 to 14.0)	15.5* (10.1 to 21.0)	24.6* (18.0 to 31.2)
Abandonment of index oral prescription	8.0 (6.6 to 9.3)	7.5 (5.2 to 9.8)	9.3 (5.7 to 12.9)	24.2* (18.1 to 30.3)	34.8* (27.6 to 42.1)	41.4* (33.3 to 49.6)
No fill of any oral anticancer agent	7.6 (6.2 to 8.9)	7.3 (5.0 to 9.6)	7.2 (4.0 to 10.4)	23.2* (17.2 to 29.1)	33.6* (26.3 to 40.9)	39.0* (30.7 to 47.3)
No fill of any oral, injected, or infusible anticancer agent	7.5 (6.2 to 8.9)	7.3 (5.1 to 9.6)	7.2 (4.0 to 10.4)	23.1* (17.2 to 29.0)	33.6* (26.3 to 40.9)	39.0* (30.6 to 47.3)
Multiple myeloma						
No. of patients	4,924	1,368	272	293	288	1,050
Reversal of index oral prescription	9.6 (7.7 to 11.5)	11.9 (9.1 to 14.6)	24.3* (18.6 to 30.0)	49.1* (38.8 to 59.3)	52.0* (44.4 to 59.7)	62.1* (56.2 to 68.0)
Delayed fill of index oral anticancer agent	3.1 (2.3 to 3.8)	4.1 (3.2 to 5.1)	11.4* (7.6 to 15.2)	11.6* (8.3 to 15.0)	10.8* (7.1 to 14.4)	17.3* (14.0 to 20.5)
Abandonment of index oral prescription	6.5 (5.0 to 7.9)	8.0 (5.7 to 10.3)	13.4* (8.6 to 18.1)	37.2* (27.7 to 46.8)	41.2* (34.2 to 48.1)	45.2* (39.2 to 51.2)
No fill of any oral anticancer agent	6.3 (4.9 to 7.7)	7.7 (5.5 to 10.0)	12.4* (7.8 to 16.9)	36.8* (27.1 to 46.4)	41.2* (34.2 to 48.1)	44.3* (38.4 to 50.2)
No fill of any oral, injected, or infusible anticancer agent	5.9 (4.6 to 7.2)	7.0 (5.0 to 9.0)	11.6* (7.0 to 16.2)	35.8* (26.0 to 45.6)	39.8* (32.7 to 47.0)	39.5* (34.0 to 45.0)
Metastatic prostate cancer						
No. of patients	3,609	740	190	287	160	731
Reversal of index oral prescription	9.4 (8.1 to 10.8)	11.8 (8.5 to 15.2)	15.5* (10.5 to 20.6)	36.8* (28.2 to 45.4)	58.1* (48.5 to 67.8)	59.2* (53.5 to 64.8)
Delayed fill of index oral anticancer agent	2.2 (1.7 to 2.8)	4.4† (2.9 to 5.9)	6.4* (3.2 to 9.6)	8.4* (4.2 to 12.6)	17.4* (10.7 to 24.1)	20.3* (16.4 to 24.2)
Abandonment of index oral prescription	7.1 (5.9 to 8.4)	7.8 (4.9 to 10.7)	9.4 (5.2 to 13.7)	28.2* (22.1 to 34.3)	39.9* (31.1 to 48.8)	38.3* (32.8 to 43.7)
No fill of any oral anticancer agent	6.9 (5.8 to 8.0)	7.4 (4.6 to 10.2)	8.9 (4.8 to 13.0)	26.1* (19.4 to 32.7)	35.0* (27.1 to 42.9)	35.2* (29.5 to 40.8)
No fill of any oral, injected, or infusible anticancer agent	6.8 (5.7 to 7.9)	7.2 (4.4 to 10.0)	8.4 (4.4 to 12.4)	25.7* (19.1 to 32.4)	34.2* (26.7 to 41.8)	33.9* (28.2 to 39.5)
Metastatic renal cell carcinoma						
No. of patients	2,192	685	233	230	355	988
Reversal of index oral prescription	19.1 (16.3 to 21.9)	15.0 (11.1 to 18.9)	20.2 (14.6 to 25.8)	35.9* (29.7 to 42.1)	58.4* (51.9 to 64.9)	77.0* (72.9 to 81.1)
Delayed fill of index oral anticancer agent	3.9 (2.9 to 4.9)	3.5 (2.2 to 4.8)	3.3 (1.1 to 5.5)	7.5* (4.3 to 10.8)	12.1* (8.2 to 15.9)	12.8* (10.0 to 15.6)
Abandonment of index oral prescription	15.2 (12.8 to 17.6)	11.5 (8.2 to 14.8)	16.9 (11.7 to 22.0)	28.3* (22.9 to 33.8)	46.2* (39.4 to 53.1)	63.9* (58.9 to 68.9)
No fill of any oral anticancer agent	14.9 (12.5 to 17.3)	11.3 (8.0 to 14.7)	17.0 (11.8 to 22.1)	27.4* (21.5 to 33.4)	45.3* (38.5 to 52.1)	62.2* (57.1 to 67.4)
No fill of any oral, injected, or infusible anticancer agent	14.7 (12.3 to 17.0)	11.4 (8.0 to 14.8)	16.6 (11.4 to 21.7)	27.5* (21.6 to 33.5)	44.8* (37.9 to 51.7)	61.1* (55.8 to 66.3)

NOTE. Reversal of index oral prescription indicates that the patient's insurance company approved the prescription but the patient did not fill it (ie, purchase it from the pharmacy), and the claim was withdrawn by the pharmacy. Delayed filling of index oral prescription indicates that the patient filled (purchased) the index oral anticancer agent within 90 days of the index prescription date. Abandonment of index oral prescription indicates that the patient had no evidence of a prescription fill for the index oral anticancer agent within 90 days of the index prescription date. No fill of any oral anticancer agent indicates that the patient had no evidence of a prescription fill for any oral anticancer agent within 90 days of the index prescription date. No fill of any oral, injectable, or infusible anticancer agent indicates that the patient had no evidence of a claim for any oral, injectable, or infusible anticancer agent within 90 days of the index prescription date.

*$P < .01$, compared with patients with out-of-pocket costs ≤ $10.

†$P < .05$, compared with patients with out-of-pocket costs ≤ $10.

‡In the case of oral anticancer agents, mail order is largely a proxy for specialty pharmacies. Other category includes retail pharmacies.

§Patients were classified into selected indication subgroups according to US Food and Drug Administration–approved indication for the index oral anticancer agent. Chronic lymphocytic leukemia agents included ibrutinib and idelalisib. Chronic myeloid leukemia agents included bosutinib, dasatinib, imatinib, nilotinib, omacetaxine, and ponatinib. Multiple myeloma agents included lenalidomide, pomalidomide, and thalidomide. Metastatic prostate cancer agents included abiraterone, enzalutamide, and nilutamide. Metastatic renal cell carcinoma agents included axitinib, pazopanib, sorafenib, and sunitinib. Everolimus was excluded from the subgroup analysis for metastatic renal cell carcinoma because it was also approved for other cancers.

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Table A4. Sensitivity Analyses: Observed Rates by Out-of-Pocket Cost Category

Modification	% of Patients				
	Reversed Claim for Index Oral Anticancer Agent*	Delayed Fill of Index Oral Anticancer Agent†	Abandonment of Index Oral Anticancer Prescription‡	No Fill of Any Oral Anticancer Agent§	No Fill of Any Oral, Injectable, or Infusible Anticancer Agent‖
Main sample (N = 38,111)					
≤ $10	12.3	3.1	9.2	9.0	8.6
$10.01-$50	15.4	4.1	11.3	11.0	10.6
$50.01-$100	21.7	5.7	16.0	15.4	14.7
$100.01-$500	44.7	8.0	36.7	35.9	34.0
$500.01-$2,000	60.8	11.5	49.3	48.4	46.6
> $2,000	67.1	17.5	49.6	48.2	45.9
Extending follow-up period for study outcomes from 90 to 180 days after index oral prescription (N = 38,111)					
≤ $10	12.3	3.6	8.6	8.4	7.9
$10.01-$50	15.4	4.7	10.6	10.3	9.7
$50.01-$100	21.7	6.4	15.3	14.5	13.6
$100.01-$500	44.7	9.6	35.0	33.8	31.4
$500.01-$,2000	60.8	13.8	47.0	45.5	42.7
> $2,000	67.1	20.3	46.8	44.5	41.9
Adding sample selection criterion requiring patients to have a diagnosis in medical claims for the cancer related to the index drug class (n = 24,956)					
≤ $10	11.2	3.1	8.1	7.9	7.5
$10.01-$50	14.0	4.0	10.0	9.7	9.1
$50.01-$100	19.7	5.4	14.3	13.4	12.5
$100.01-$500	42.4	8.6	33.8	32.7	30.7
$500.01-$2,000	59.9	12.6	47.3	46.1	43.6
> $2,000	66.2	17.7	48.5	46.8	43.6
Substituting sample selection criterion requiring more frequent (ie, quarterly) prescription fill activity and medical activity in the pre- and postindex periods (n = 18,450)					
≤ $10	11.9	3.0	8.8	8.6	8.6
$10.01-$50	15.2	4.5	10.6	10.5	10.5
$50.01-$100	21.4	6.1	15.3	14.8	14.8
$100.01-$500	43.8	8.6	35.2	34.7	34.7
$500.01-$2,000	61.3	13.3	48.0	47.1	47.1
> $2,000	68.2	18.3	49.9	48.8	48.8
Eliminating sample selection criteria requiring prescription or medical activity in pre- and postindex periods (n = 75,176)					
≤ $10	13.7	3.1	10.6	10.4	10.2
$10.01-$50	17.4	4.6	12.9	12.6	12.3
$50.01-$100	25.2	5.8	19.4	18.9	18.5
$100.01-$500	46.6	8.2	38.3	37.5	36.4
$500.01-$2,000	62.4	11.1	51.2	50.3	49.1
> $2,000	69.5	15.4	54.1	52.8	51.4
Patients in states with chemotherapy parity law during the index year (n = 27,332)					
≤ $10	12.3	3.1	9.2	9.0	8.7
$10.01-$50	14.4	4.1	10.3	10.1	9.7
$50.01-$100	21.4	4.9	16.5	15.9	15.1
$100.01-$500	43.2	8.1	35.0	34.5	32.6
$500.01-$2,000	60.8	10.9	49.9	48.9	46.8
> $2,000	66.3	17.8	48.5	47.3	44.8
Patients in states without chemotherapy parity law during the index year (n = 10,779)					
≤ $10	12.1	3.0	9.1	8.9	8.6
$10.01-$50	17.6	4.2	13.4	13.1	12.5
$50.01-$100	22.2	7.4	14.8	14.2	13.9
$100.01-$500	48.5	7.6	40.8	39.3	37.6
$500.01-$2,000	60.7	13.0	47.8	47.0	46.0
> $2,000	69.2	16.7	52.5	50.7	49.0

NOTE. All estimates are unadjusted for any covariates.
*Patient's insurance company approved the prescription but the patient did not fill it (ie, purchase it from the pharmacy), and the claim was withdrawn by the pharmacy.
†Patient filled (purchased) the index oral anticancer agent within 90 days of the index prescription date.
‡Patient had no evidence of a prescription fill for the index oral anticancer agent within 90 days of the index prescription date.
§Patient had no evidence of a prescription fill for any oral anticancer agent within 90 days of the index prescription date.
‖Patient had no evidence of a claim for any oral, injectable, or infusible anticancer agent within 90 days of the index prescription date.

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Table A5. Sensitivity Analyses: Adjusted Odds Ratios

Modification	Odds Ratios (95% CI)				
	Reversed Claim for Index Oral Anticancer Agent*	Delayed Fill of Index Oral Anticancer Agent†	Abandonment of Index Oral Anticancer Prescription‡	No Fill of Any Oral Anticancer Agent§	No Fill of Any Oral, Injectable, or Infusible Anticancer Agent‖
Main sample					
≤ $10	Reference	Reference	Reference	Reference	Reference
$10.01-$50	1.11 (0.93 to 1.32)	1.30¶ (1.05 to 1.60)	1.07 (0.87 to 1.31)	1.06 (0.86 to 1.32)	1.06 (0.86 to 1.32)
$50.01-$100	1.58# (1.35 to 1.85)	1.91# (1.45 to 2.50)	1.45# (1.22 to 1.71)	1.41# (1.19 to 1.67)	1.41# (1.18 to 1.68)
$100.01-$500	5.09# (3.95 to 6.55)	2.99# (2.31 to 3.86)	4.87# (3.84 to 6.18)	4.80# (3.75 to 6.14)	4.56# (3.53 to 5.89)
$500.01-$2,000	9.34# (7.90 to 11.05)	4.78# (3.92 to 5.82)	7.64# (6.33 to 9.23)	7.49# (6.23 to 8.99)	7.16# (5.94 to 8.64)
> $2,000	16.49# (13.62 to 19.96)	6.76# (5.40 to 8.47)	11.16# (9.27 to 13.44)	10.82# (8.97 to 13.06)	9.97# (8.25 to 12.06)
Extending follow-up period for study outcomes from 90 to 180 days after index oral prescription					
≤ $10	Reference	Reference	Reference	Reference	Reference
$10.01-$50	1.11 (0.93 to 1.32)	1.28¶ (1.06 to 1.53)	1.07 (0.86 to 1.32)	1.06 (0.85 to 1.32)	1.06 (0.85 to 1.33)
$50.01-$100	1.58# (1.35 to 1.85)	1.84# (1.44 to 2.35)	1.45# (1.22 to 1.72)	1.40# (1.18 to 1.67)	1.41# (1.18 to 1.69)
$100.01-$500	5.09# (3.95 to 6.55)	3.11# (2.37 to 4.09)	4.77# (3.79 to 6.01)	4.68# (3.68 to 5.95)	4.38# (3.42 to 5.62)
$500.01-$2,000	9.34# (7.90 to 11.05)	5.02# (4.17 to 6.05)	7.28# (5.98 to 8.87)	7.09# (5.83 to 8.62)	6.60# (5.43 to 8.03)
> $2,000	16.49# (13.62 to 19.96)	6.94# (5.56 to 8.65)	10.65# (8.75 to 12.96)	10.11# (8.30 to 12.33)	9.24# (7.57 to 11.28)
Adding sample selection criterion requiring patients to have a diagnosis in medical claims for the cancer related to the index drug class					
≤ $10	Reference	Reference	Reference	Reference	Reference
$10.01-$50	1.09 (0.90 to 1.33)	1.23 (0.95 to 1.59)	1.07 (0.84 to 1.36)	1.07 (0.84 to 1.36)	1.06 (0.83 to 1.36)
$50.01-$100	1.58# (1.31 to 1.90)	1.78# (1.25 to 2.52)	1.48# (1.23 to 1.79)	1.41# (1.16 to 1.72)	1.39# (1.13 to 1.71)
$100.01-$500	5.30# (4.09 to 6.86)	3.14# (2.42 to 4.07)	5.08# (3.96 to 6.52)	4.99# (3.84 to 6.49)	4.73# (3.59 to 6.24)
$500.01-$2,000	10.02# (8.25 to 12.17)	5.21# (4.18 to 6.51)	8.03# (6.48 to 9.93)	7.83# (6.37 to 9.61)	7.41# (5.99 to 9.18)
> $2,000	16.66# (13.65 to 20.34)	7.02# (5.57 to 8.86)	11.30# (9.25 to 13.81)	10.91# (8.88 to 13.39)	9.84# (7.99 to 12.13)
Substituting sample selection criterion requiring more frequent (ie, quarterly) prescription fill activity and medical activity in the pre- and postindex periods					
≤ $10	Reference	Reference	Reference	Reference	Reference
$10.01-$50	1.14 (0.94 to 1.39)	1.49# (1.18 to 1.88)	1.04 (0.82 to 1.32)	1.05 (0.83 to 1.34)	1.04 (0.82 to 1.33)
$50.01-$100	1.68# (1.35 to 2.09)	2.19# (1.53 to 3.13)	1.47# (1.15 to 1.89)	1.44# (1.11 to 1.86)	1.47# (1.14 to 1.90)
$100.01-$500	5.35# (4.00 to 7.17)	3.33# (2.37 to 4.68)	4.99# (3.72 to 6.70)	4.99# (3.68 to 6.75)	4.82# (3.56 to 6.51)
$500.01-$2,000	10.16# (8.04 to 12.84)	5.80# (4.44 to 7.59)	7.66# (6.07 to 9.67)	7.53# (5.98 to 9.48)	7.13# (5.61 to 9.06)
> $2,000	18.14# (14.55 to 22.60)	7.40# (5.93 to 9.24)	11.74# (9.43 to 14.62)	11.52# (9.29 to 14.28)	10.33# (8.32 to 12.83)
Eliminating sample selection criteria requiring prescription or medical activity in pre- and postindex periods					
≤ $10	Reference	Reference	Reference	Reference	Reference
$10.01-$50	1.18¶ (1.00 to 1.38)	1.46# (1.24 to 1.71)	1.10 (0.91 to 1.33)	1.09 (0.90 to 1.33)	1.09 (0.90 to 1.32)
$50.01-$100	1.71# (1.51 to 1.94)	1.92# (1.54 to 2.39)	1.59# (1.40 to 1.80)	1.57# (1.38 to 1.78)	1.57# (1.38 to 1.79)
$100.01-$500	4.94# (3.94 to 6.20)	2.92# (2.48 to 3.43)	4.61# (3.68 to 5.79)	4.53# (3.60 to 5.70)	4.42# (3.49 to 5.58)
$500.01-$2,000	9.08# (7.64 to 10.79)	4.34# (3.67 to 5.13)	7.38# (6.17 to 8.82)	7.25# (6.06 to 8.67)	7.02# (5.85 to 8.42)
> $2,000	16.00# (13.31 to 19.23)	5.69# (4.83 to 6.70)	11.18# (9.23 to 13.54)	10.86# (8.94 to 13.19)	10.30# (8.45 to 12.55)

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Table A5. Sensitivity Analyses: Adjusted Odds Ratios (continued)

Modification	Odds Ratios (95% CI)				
	Reversed Claim for Index Oral Anticancer Agent*	Delayed Fill of Index Oral Anticancer Agent†	Abandonment of Index Oral Anticancer Prescription‡	No Fill of Any Oral Anticancer Agent§	No Fill of Any Oral, Injectable, or Infusible Anticancer Agent‖
Models including indicator of patients in states with chemotherapy parity law during the index year					
≤ $10	Reference	Reference	Reference	Reference	Reference
$10.01-$50	1.10 (0.93 to 1.31)	1.29¶ (1.05 to 1.59)	1.06 (0.87 to 1.31)	1.06 (0.86 to 1.31)	1.06 (0.86 to 1.32)
$50.01-$100	1.58# (1.35 to 1.85)	1.90# (1.45 to 2.50)	1.45# (1.22 to 1.71)	1.41# (1.19 to 1.67)	1.41# (1.18 to 1.68)
$100.01-$500	5.08# (3.95 to 6.55)	2.98# (2.31 to 3.85)	4.87# (3.84 to 6.18)	4.80# (3.75 to 6.14)	4.56# (3.53 to 5.89)
$500.01-$2,000	9.36# (7.92 to 11.06)	4.78# (3.92 to 5.82)	7.65# (6.34 to 9.24)	7.50# (6.24 to 9.01)	7.18# (5.95 to 8.66)
> $2,000	16.50# (13.63 to 19.97)	6.76# (5.40 to 8.47)	11.17# (9.28 to 13.45)	10.83# (8.97 to 13.07)	9.98# (8.26 to 12.06)
Models including indicators of month of index drug					
≤ $10	Reference	Reference	Reference	Reference	Reference
$10.01-$50	1.11 (0.93 to 1.33)	1.30¶ (1.05 to 1.61)	1.07 (0.87 to 1.32)	1.07 (0.86 to 1.32)	1.07 (0.86 to 1.33)
$50.01-$100	1.58# (1.35 to 1.85)	1.89# (1.44 to 2.48)	1.45# (1.22 to 1.71)	1.41# (1.19 to 1.67)	1.41# (1.18 to 1.68)
$100.01-$500	5.15# (4.00 to 6.64)	2.98# (2.31 to 3.84)	4.93# (3.88 to 6.25)	4.85# (3.78 to 6.21)	4.61# (3.56 to 5.96)
$500.01-$2,000	9.27# (7.82 to 10.98)	4.68# (3.84 to 5.70)	7.58# (6.25 to 9.18)	7.42# (6.15 to 8.95)	7.10# (5.86 to 8.60)
> $2,000	16.06# (13.19 to 19.54)	6.58# (5.23 to 8.29)	10.89# (9.00 to 13.17)	10.54# (8.69 to 12.79)	9.72# (8.00 to 11.82)

NOTE. All estimates are adjusted for all covariates listed in Table 2.
*Patient's insurance company approved the prescription but the patient did not fill it (ie, purchase it from the pharmacy), and the claim was withdrawn by the pharmacy.
†Patient filled (purchased) the index oral anticancer agent within 90 days of the index prescription date.
‡Patient had no evidence of a prescription fill for the index oral anticancer agent within 90 days of the index prescription date.
§Patient had no evidence of a prescription fill for any oral anticancer agent within 90 days of the index prescription date.
‖Patient had no evidence of a claim for any oral, injectable, or infusible anticancer agent within 90 days of the index prescription date.
#$P < .01$.
¶$P < .05$.

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