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Factors Affecting Usage Levels and Trends of Innovative Oncology Drugs Upon and After Reimbursement Under Taiwan National Health Insurance: Interrupted Time Series Analysis

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Healthcare expenditure on pharmaceuticals, especially innovative oncology drugs, is escalating. Current knowledge on this topic is largely limited to studies conducted upon reimbursement of new drugs. We investigated how endogenous factors (e.g., changed reimbursement criteria, such as an expanded indication) and exogenous factors (e.g., competing drugs) affect the level and trends of innovative oncology drug utilization in the Taiwan National Health Insurance (NHI) system, both upon reimbursement and afterward. This retrospective longitudinal study analyzed monthly data (January 2009 to December 2014) from the NHI Research Database on the consumption (prescribing volume) of 15 innovative oncology drugs reimbursed by the NHI between 2007 and 2013. Effects of endogenous and exogenous factors on drug utilization were evaluated using interrupted time series analyses. In segmented regression analyses, changed drug prescribing volume after the indication expanded (endogenous factor) was statistically significant; however, drug volume did not change significantly after prescription restrictions changed. First-competitors and non-first-competitors (exogenous factors) were significantly associated with drug prescription levels or utilization rates. Taking sorafenib as an example, the post-reimbursement drug prescribing volume did not change significantly after its therapy line changed (endogenous factor), whereas the reimbursement of first-competitors (exogenous factor) was significantly associated with a lower level or usage rate of sorafenib. Utilization of innovative oncology drugs in Taiwan changed dramatically after NHI reimbursement, driven largely by expanded indications and new competitors. Drug utilization evaluations should investigate both endogenous and exogenous factors.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?
☑ Influences on the utilization rates of drugs after they become reimbursed under a national health insurance system are not well understood.

WHAT QUESTION DID THIS STUDY ADDRESS?
☑ This retrospective longitudinal study analyzed monthly data (January 2009 to December 2014) from the Taiwan National Health Insurance (NHI) Research Database on the consumption (prescribing volume) of 15 innovative oncology drugs reimbursed by the NHI between 2007 and 2013. Effects of endogenous and exogenous factors on drug utilization were evaluated using interrupted time series analyses.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?
☑ Prescribing volumes of innovative oncology drugs changed dynamically after reimbursement under Taiwan NHI, and were influenced by both endogenous factors (e.g., expanded indication) and exogenous factors (e.g., drug competition).

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?
☑ As the indications of most new oncology drugs expand after initial reimbursement, payers should take great care in setting the initial price for a new drug and evaluate post-reimbursement drug use assiduously, taking into due consideration the effects of both endogenous and exogenous factors.

The incidence of cancer is rising worldwide,[1–3] exacerbating substantial healthcare burdens, including high mortality and poor quality of life. Consequently, research and development

of oncology drugs has increased in parallel to fulfil major unmet medical needs.[4–6] For example, innovative targeted therapy has revolutionized the treatment of metastatic renal

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cell carcinoma (mRCC) over recent decades.[7] The Taiwan National Health Insurance Administration (NHIA) reimbursed five new targeted agents from October 2009 to December 2013, including the tyrosine kinase inhibitors sorafenib, sunitinib, and pazopanib, and the mammalian target of rapamycin inhibitors everolimus and temsirolimus.

Despite undoubted clinical benefits, the high cost of new anticancer agents presents significant challenges concerning healthcare budgeting and affordability.[8–11] Hence, decision making about whether or not to reimburse innovative oncology drugs has garnered increasing global research attention.[12–16] To maintain the financial sustainability of healthcare systems, it is crucial not to overlook drug utilization subsequent to reimbursement, especially regarding expensive new oncology drugs.

The post-reimbursement utilization of innovative oncology drugs may be influenced by various factors. For example, most anticancer agents are approved for expanded indications as new evidence becomes available; imatinib, which the US Food and Drug Administration first approved for chronic myeloid leukemia in 2001, has since gained 9 additional indications.[17] Moreover, most oncology drugs are reimbursed conditionally,[18] with public-sector funding under specified circumstances, such as for certain patient groups or indications, or upon failure of prior therapy lines. Therefore, the initially reimbursed indication, therapy line, or prescription restriction of a new drug will likely change, and all such changes will affect its utilization. Another factor influencing drug utilization is intensified competition between drugs within a class.

The determinants of drug utilization under the Taiwan National Health Insurance (NHI) can be broadly classified as either endogenous—changes related to the drug itself, or exogenous—extrinsic environmental changes. Endogenous factors in Taiwan include the NHI reimbursement criteria, which impose various restrictions, such as specifying the indication or population, prior authorization, stepwise therapy, quotas, and suchlike. The Taiwan NHIA applies national reimbursement criteria to restrict the use of reimbursed drugs with the aims of reducing inappropriate use, controlling budgets, and improving the efficiency of pharmacotherapy across the healthcare system. Prescribers must meet these criteria and the NHIA tracks prescribing and related physician request justifications to police appropriate drug use. As these reimbursement criteria detail the coverage restrictions of innovative oncology drugs, we hypothesized that changes to these criteria (endogenous factor) would be associated with changed utilization of these drugs. Under Taiwan's universal healthcare coverage scheme,[19–21] new drugs are specifically required to compete with other indicated drugs (exogenous factor) in a single national market. We hypothesized that reimbursement of a new drug may diminish utilization of other drugs in the same therapeutic class.

Understanding endogenous and exogenous influences on the use of expensive oncology drugs is crucial to informing coverage and reimbursement decisions by payers, besides benefiting utilization management in oncology; it is also important to pharmaceutical firms for shaping marketing strategies for their products. However, this remains a major knowledge gap. First, most studies have focused around the time of drug reimbursement—none have investigated dynamic post-reimbursement changes in drug utilization. Second, there is little empirical evidence about how these factors affect the utilization of innovative oncology drugs in Taiwan. Third, previous studies of drug competition have concentrated on generic competitors, rather than newly reimbursed drugs. Last, we know of no comprehensive investigation of the impacts of both endogenous and exogenous factors on drug utilization. Hence, the objectives of this study were to examine dynamic changes in the utilization of innovative oncology drugs, and to investigate whether and how their post-reimbursement utilization was associated with changed national reimbursement criteria (endogenous factors), or new drug competition (exogenous factor).

METHODS

Taiwan NHI system

In Taiwan, all new drugs are evaluated and get approved by the Taiwan Food and Drug Administration (TFDA). Subsequently, the reimbursement of a new drug is decided by the NHIA.[19] Currently, the Pharmaceutical Benefit and Reimbursement Scheme joint committee (PBRS) Joint Committee, a 29-member panel comprising government officials, health professionals, manufacturers, and members of the public, as the final arbiter of suitability for NHI reimbursement. Besides reimbursement decisions, the PBRS also sets the final NHI reimbursement price. Any expansions or contractions in the label should be reviewed by the PBRS before it can be reimbursed by the NHI. Off-label prescriptions outside of the reimbursement scheme are not allowed. Routine audit for off-label prescription is conducted by the NHIA and the corresponding fine is issued to contracted medical institutions or physicians.[20,21]

Sample selection

We identified new oncology drugs that the Taiwan NHI system reimbursed between 2007 and 2013. Innovative oncology drugs were defined as new molecular entities in the World Health Organization Anatomical Therapeutic Chemical[22] groups L01 (antineoplastic agents) and L04 (immunosuppressants) with an indication for cancer. We excluded drugs with a new dosage, formulation, or combination, prescriptions of oncology drugs for non-cancer conditions, and designated orphan pharmaceuticals.

Our protocol comprised an endogenous factor analysis, an exogenous factor analysis, and a comprehensive integrated analysis. The endogenous factor analysis included innovative oncology drugs with changed reimbursement criteria. We selected mRCC drugs as the therapeutic class for exogenous factor analysis. The study enrolled people ≥ 20 years old who were registered with mRCC in the Taiwan Cancer Registry, and had been treated with relevant innovative oncology drugs (sorafenib, sunitinib, everolimus, pazopanib, and temsirolimus), immunotherapeutic drugs (interferon-alfa and interleukin-2), or cytotoxic agents (gemcitabine). Sorafenib, was selected as the exemplar for comprehensive analysis, because it was subject to coexisting endogenous and exogenous influences during the study period.

Study design and data source

The Taiwan NHI Research Database includes complete information on cancer registration and claims for visits, procedures, and prescriptions covering > 99% of the national population. We retrieved all monthly claims data on prescribing volume of study drugs with follow-up data for ≥ 1 year, from January 1, 2009, and December 31, 2014, for interrupted time series analysis.[23,24] For each prescription, we also retrieved its corresponding diagnosis codes for information on its indications. Drug reimbursement information and changes to national reimbursement criteria were retrieved from the NHIA website (https://www.nhi.gov.tw/).

Endogenous and exogenous factors

We defined intervening factors and observed how they affected drug utilization during the 6-year study period. Endogenous intervention was defined as changed NHI reimbursement criteria, in four categories: (i) expanded indication; (ii) change from later-line to earlier-line therapy; (iii) changed prescribing restriction on prior authorization, stepwise therapy, or quota; and (iv) multiple factors (e.g., changed therapy line and prescribing restriction). Exogenous intervention constituted NHI reimbursement of a competitor drug for mRCC and was classified into two types, first-competitor or non-first-competitor, based on similarities of the compared drugs, including mechanism, dosage form, and therapy line. **Table 1** and **Table S2** summarize the drug information and competitor relationships.

Statistical analysis

All analyses were performed using SAS, version 9.4 (SAS Institute, Cary, NC), with a statistical significance threshold of $P < 0.05$. Segmented regression was used to analyze time series data[23,24] and to examine how the defined interventions affected the prescribing volume of individual innovative oncology drugs after vs. before such changes were introduced. We studied intervention in three ways: (i) change in level immediately after the intervention; (ii) difference between pre-intervention and postintervention slopes; and (iii) absolute and relative changes with 95% confidence intervals for each outcome 3 months after the intervention.

Prescribing volume data for endogenous factor analysis were calculated in units of tablet, capsule, or vial. To compare the consumption volume of drugs within a class, prescribing volume data in exogenous factor analysis were translated into the average daily dose, which was assumed to be the average daily dose used to treat an adult patient with mRCC.

Because error terms in time series data may be correlated, we used the Durbin–Watson test to check every model for autocorrelation and, if autocorrelation was detected, estimated the regression parameters controlled for autocorrelation.

RESULTS

Drug characteristics

Table 1 details the characteristics of 15 innovative oncology drugs, covering 14 therapeutic classes in oncology, that we identified. The earliest reimbursed drugs were bortezomib and erlotinib, in June 2007, whereas the last was azacytidine, in January 2013. All except azacitidine and bendamustine are targeted therapies; four (bortezomib, cetuximab, everolimus, and thalidomide) act on new targets, and the other 11 drugs are next-generation drugs with similar mechanisms of action to already reimbursed drugs.

Endogenous factor analysis. Endogenous factor analysis included 10 drugs with changed NHI reimbursement criteria, of which bendamustine, bevacizumab, dasatinib, everolimus, and nilotinib had their reimbursement criteria changed once until December 31, 2014, whereas the criteria for sorafenib, cetuximab, sunitinib, bortezomib, and erlotinib changed three times. **Table 2** summarizes the effects of changing various NHI reimbursement criteria on the prescribing volume of these drugs; indication expansion had the most significant effect on prescribing volume. For example, sorafenib prescriptions increased dramatically when its indication expanded to include metastatic hepatocellular carcinoma, in August 1, 2012, with a significantly changed level upon intervention and significantly increased absolute change 3 months postintervention. (**Figure 1h-2**, **Table S1**). However, indication expansion did not always seem to influence drug prescribing volume; there were no significant changes in level or trend of bendamustine prescription when its indication expanded to non-Hodgkin's lymphoma, (**Figure 1g**, **Table S1**).

Among four line of therapy changes, only one, cetuximab from second-line to first-line therapy for KRAS wild-type metastatic colorectal cancer, significantly increased level and trend in prescribing volume (**Figure 1c-3**, **Table S1**).

Prescribing restriction change had little apparent impact on drug prescribing volume; only two of eight such interventions were associated with significant level or trend changes (**Figure 1c-2**, **b-5**, **Table S1**). For example, cetuximab prescribing volume declined considerably after restriction became stricter.

Sunitinib is an example of multiple changes; in January, 2010, its indication expanded to mRCC and the prescribing restriction for gastrointestinal stromal tumor was also relaxed. These changes resulted in significant increased prescribing volume (**Figure 1i-2**, **Table S1**). **Table S1** further summarizes the effects of each endogenous intervention.

Exogenous factor analysis. Table 2 summarizes the exogenous factor analysis results; both first-competitors and non-first-competitors significantly affected the level/trend of prescribing volume or the absolute/relative change 3 months postintervention.

Figure 2 depicts trends in prescribing volume over the study period. When sunitinib was covered for first-line therapy of mRCC, its monthly prescribing volume rose sharply for 3 years, followed by a marked decline. However, not all drug competition led to declining prescribing volume. For example, when the NHIA listed everolimus as a third-line therapy for mRCC (following sunitinib and sorafenib failure), sorafenib prescribing volume increased (**Figure 2a**). **Table S2** further summarizes the effects of each exogenous intervention.

Table 1 Drug characteristics for 15 innovative oncology drugs

Drug	Date reimbursed	Indication[a]	Targeted agent (yes/no)	First-in-class (yes/no)
Bortezomib[b]	6/1/2007	Multiple myeloma	Yes	Yes (proteasome inhibitor)
	2/1/2009	Mantle cell lymphoma		
Erlotinib[b]	6/1/2007	Metastatic/locally advanced metastatic non-small cell lung cancer	Yes	No
Cetuximab[b]	3/1/2007	Metastatic colorectal cancer	Yes	Yes (epidermal growth factor receptor inhibitor)
	7/1/2009	Locally/regionally advanced squamous cell carcinoma of the head and neck (excluding nasopharyngeal carcinoma)		
Bevacizumab[b]	6/1/2011	Metastatic colorectal cancer	Yes	No
	5/1/2012	Glioblastoma multiforme		
Dasatinib[b]	1/1/2009	Philadelphia chromosome positive chronic myelogenous leukemia	Yes	No
Nilotinib[b]	6/1/2009	Philadelphia chromosome positive chronic myelogenous leukemia	Yes	No
Bendamustine[b]	10/1/2012	Chronic lymphoid leukemia	No	No
	2/1/2013	Non-Hodgkin's lymphoma		
Sorafenib[b,c,d]	10/1/2009	Metastatic renal cell carcinoma (first-line if unsuited or intolerant to cytokine therapy)	Yes	No
	8/1/2012	Unresectable hepatocellular carcinoma		
Sunitinib[b,c]	2/1/2009	Gastrointestinal stromal tumor: after disease progression on, or intolerance to, imatinib	Yes	No
	1/1/2010	Metastatic renal cell carcinoma (first-line)		
	5/1/2012	Unresectable, locally advanced/metastatic pancreatic neuroendocrine tumor		
Everolimus[b,c]	2/1/2011	Metastatic renal cell carcinoma (second-line after sorafenib or sunitinib)	Yes	Yes (mammalian target of rapamycin inhibitor)
	1/1/2013	Unresectable, locally advanced/metastatic pancreatic neuroendocrine tumor		
Pazopanib[c]	2012/8/1	Metastatic renal cell carcinoma (first-line)	Yes	No
Temsirolimus[c]	2012/1/1	Metastatic renal cell carcinoma (for high-risk patients)	Yes	No
Azacitidine	2013/1/1	Myelodysplastic syndrome	No	No
Lenalidomide	2012/12/1	Multiple myeloma	Yes	No
Thalidomide	2009/7/1	Multiple myeloma	Yes	Yes (angiogenesis inhibitor)

[a]Reimbursed under Taiwan National Health Insurance.
[b]Included in endogenous factor analysis.
[c]Included in exogenous factor analysis.
[d]Included in comprehensive analysis.

Integrated analysis of endogenous and exogenous factors

Considering both endogenous and exogenous factors in the example of sorafenib, only reimbursement of sunitinib and pazopanib, both first-competitors, contributed to decreasing its prescribing volume and level (**Table 3** and **Figure 3**), whereas endogenous factors had little effect.

DISCUSSION

This study revealed dynamic changes in the utilization of innovative oncology drugs after they became reimbursed, which were attributable to both endogenous factors (changed reimbursement criteria) and exogenous factors (drug competition). The reimbursement criteria of most innovative oncology drugs changed after initial reimbursement, and drug competition in mRCC intensified during the study period. These findings support our hypotheses that changed national reimbursement criteria and drug competition influence the utilization of innovative oncology drugs. Endogenous factor analysis showed that the indications of innovative oncology drugs often expanded, and the impact of this change on drug prescribing volume was more significant than other kinds of changes to national reimbursement criteria. Exogenous factor analysis showed that reimbursement of a competitor drug can significantly affect prescribing volume of a study drug.

Previous studies have attributed growth in the market for targeted cancer drugs to expanding indications for these drugs,[17] but we discovered that expanded indications did not always result in increased prescribing volume. This relationship may vary between indications and countries; for example, a new indication for a patient population smaller than that of the original indication, would probably not significantly increase the prescribing volume, as we found when bendamustine was indicated for non-Hodgkin's lymphoma, which affects relatively few patients in Taiwan (**Figure 1g**, **Table S1**).[3]

Table 2 Segmented linear regression analysis results for postintervention changes in prescribing volume

Data show numbers (%)	Changed reimbursement criteria[a]			Drug competition[b]		
Nature of change	Expanded indication	Therapy line	Prescription restriction	Multiple	First-competitor	Non-first-competitor
Level/trend significant[c]						
3 months postintervention						
Significant[d]	4	1	0	2	2	2
Nonsignificant	1	0	2	0	0	2
Level/trend nonsignificant[e]						
3 months postintervention						
Significant	0	1	1	0	0	3
Nonsignificant[f]	3	2	5	1	1	0
Total	8/23 (34.8)	4/23 (17.4)	8/23 (34.8)	3/23 (13.0)	3/10 (30.0)	7/10 (70.0)

[a]Results of individual interventions are presented in **Table S1**.
[b]Results of individual interventions are presented in **Table S2**.
[c]Significant change in level or trend upon intervention.
[d]Significant change in level or trend upon intervention *and* the significant relative change or absolute change 3 months postintervention.
[e]Nonsignificant change in level or trend upon intervention.
[f]Nonsignificant change in level or trend upon intervention *and* nonsignificant relative or absolute change 3 months postintervention.

Conversely, sorafenib's new indication for metastatic hepatocellular carcinoma significantly increased prescription volume (**Figure 1h**, **Table S1**), because hepatocellular carcinoma has been the third or fourth most common cancer in Taiwan for several decades.[3,25]

Although we also expected changed therapy line, all of which were from later to earlier lines, to increase prescribing volume, only one of four such interventions led to a significantly increased level and trend in prescriptions (**Figure 1c-3**, **Table S1**). The explanation might be that patients must meet specific criteria for first-line therapy. For example, the first indication change for bortezomib in multiple myeloma was from third-line to second-line, but it could only be prescribed to patients unsuitable for, or intolerant to, bone marrow therapy. In addition, when it subsequently became first-line therapy, only candidates for bone marrow therapy younger than 65 years were eligible. Neither intervention was associated with a significant rise in prescribing volume (**Figure 1a-1 and a-3**, **Table S1**).

Contrary to the reasonable expectation that relaxation of prescribing restrictions would increase drug prescribing volume, and vice versa, most restriction changes, which were to add new restrictions, had no significant effect on drug prescribing volume. Again, it seems that the effect of national prescribing restriction change may vary between countries and disease areas. A study in Korea found that prescribing restriction decreased daily utilization of antihypertensive drugs,[26] whereas United States investigators reported that prescribing restrictions did not significantly reduce antipsychotics' utilization[27]; another study found that relaxing prescribing restriction caused a rise in statin prescriptions.[28]

Like Taiwan, healthcare systems worldwide are developing and implementing management strategies intended to control utilization and costs of oncology drugs[5,29,30]; these policies include restrictive formularies, prior authorization, stepwise therapy, quotas, and clinical pathways, some of which resemble Taiwan's national reimbursement criteria. As few studies to date have investigated the effects of these utilization management policies, ours provides valuable information for other healthcare payers.

In the crowded mRCC market, with five innovative oncology drugs covered by Taiwan NHIA during this study period, competition has extremely significant effects. Exogenous factor analysis produced interesting results. First, sunitinib, the first "initial therapy" for mRCC, had first-to-market advantage. Sorafenib, as a second-line therapy, was the first innovative oncology drug that the NHIA reimbursed for mRCC. However, as sunitinib was already listed, its prescribing volume exceeded that of sorafenib (**Figure S1**). Although a previous study found that the order of market entry would influence peak share, it disregarded the therapy line of the entrants.[31] Our study indicates that the first frontline therapy would gain market advantage.

Unexpectedly, we found that even reimbursement of a non-first-competitor drug significantly affected drug prescribing volume, also that drug competition led drug prescribing volume to not only decline but also to increase. For instance, after everolimus became reimbursed as third-line therapy for mRCC, sorafenib prescribing volume increased significantly (**Figure 2a**, **Table S2**), suggesting that entry of a subsequent agent can boost utilization of a frontline agent. The availability of an alternative if frontline therapy fails, may encourage physicians to start earlier line therapy as soon as possible.

Finally, comprehensive analysis of sorafenib showed that drug competition had a larger effect than that of changed national reimbursement criteria. Furthermore, first-competitors had larger impacts on sorafenib prescribing volume than did non-first-competitors; further investigation on other drugs is warranted.

Strengths

First, this is the first study that we are aware of to use interrupted time series to investigate the effects of national criteria changes and new drug competition on oncology
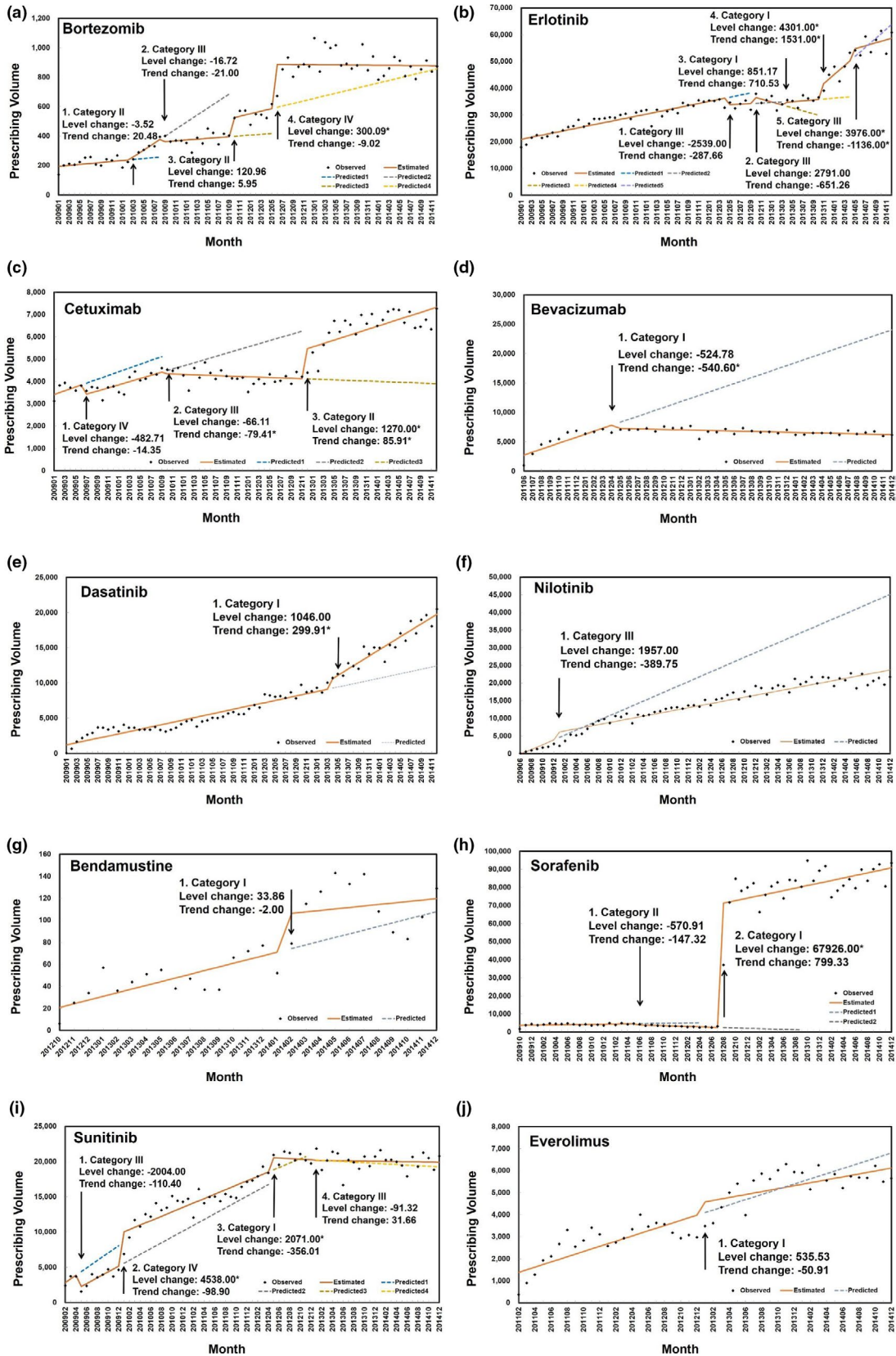
Figure 1 Trends in prescribing volumes of study drugs before and after the intervention of changed reimbursement criteria (endogenous factors). Categories of change: (I) expanded indication; (II) therapy line; (III) prescribing restriction; and (IV) multiple. *$P < 0.05$.
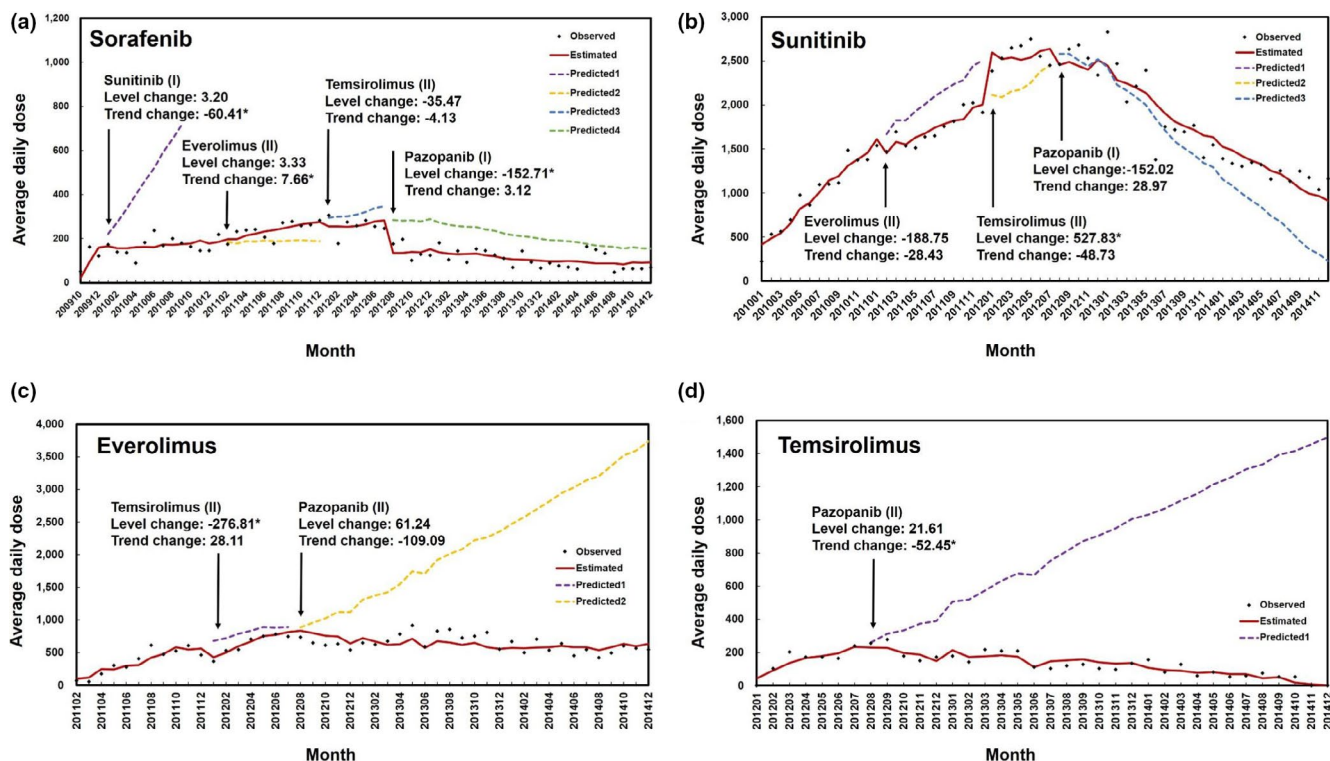
Figure 2 Trends in prescribing volumes of study drugs before and after the intervention of drug competition (exogenous factor). (I) First-competitor relationship between an index drug and an introduced drug; (II) non-first-competitor relationship between an index drug and an introduced drug. *P < 0.05.

drug utilization. Interrupted time series analyses are considered the strongest quasi-experimental design in intervention research[32] and can adjust for the baseline level and trend to evaluate the pure effects of an intervention.[23] Second, although there have been some studies of the effects of policy interventions—guideline changes, coverage restrictions, prescribing restriction, and prior authorization—on drug utilization, the results varied by therapeutic class and healthcare system.[27,28,33,34] Moreover, most previous studies focused on the effects of generic drug competition.[35,36] As ever more innovative oncology drugs are developed and marketed, the effect of new drug competition cannot be ignored. Previous studies of either policy or drug competition, also lacked a comprehensive integrated evaluation. Therefore, our study provides rare evidence about the combined effects of policy and competition on the utilization of innovative oncology drugs. Third, our measures using actual insurance claims data reflect true NHIA-funded prescribing volume, making the results beneficial to decision making by national payers.

Limitations

If interventions investigated by interrupted time series analysis occur simultaneously, it is difficult to ascertain which was more important for the changes in prescription volume. As with the interventions classified into multiple types (**Figure 1a-4**, **c-1**, **i-2**, **Table S1**), these results just reflect mixed effects of "co-intervention." Nevertheless, there are two major rationales why we adopted the time-series models rather than the difference-in-differences approach in this study. First, as our studied drugs are mainly novel oncologic agents, there were no appropriate comparators to be identified when they were first reimbursed by the NHIA, which make the difference-in-differences approach unfeasible. Second, as we intend to capture the "dynamic changes" after a drug was reimbursed, the time-series models better suit our study objective. Another potential limitation is that including the prescribing volume data during the first few months after drug reimbursement in segmented regression analysis may lead the slope and predicted volume to be overestimated. If numerous patients are waiting to use a forthcoming drug, rapidly rising the prescribing volume during the first few months post-reimbursement might result in overestimation of the slope and predicted volume and a negative level change (estimated volume minus predicted volume). In the case of bevacizumab, the expanded indication for glioblastoma, counterintuitively resulted in a decreased level and decline in prescribing volume (**Figure 1d**). Third, other factors besides changed national reimbursement criteria and drug competition, such as price-volume agreements, may also influence drug utilization.[37,38] Price-volume agreement links pricing to the quantity consumed for budget control. The Taiwan NHI system makes price-volume agreements with pharmaceutical firms, and negotiates the initial list price and volume threshold for a new drug. If the total sales volume exceeds this threshold, the pharmaceutical firm rebates a portion of sales to the NHI system. Consequently, a price-volume agreement limits growth in drug prescribing volume. Unfortunately, it is unknown which drugs are covered by price-volume agreements, as this information is kept

Table 3 Segmented linear regression model results for comprehensive analysis[a]

Intervention date	Intervention	Change upon intervention		Change 3 months postintervention	
		Level (95% CI)	Trend (95% CI)	Absolute (95% CI)	Relative (95% CI)
1/1/2010	Sunitinib[b] (first-competitor[c])	1.7 (−82.7, 86.1)	−58.9* (−110.8, −7.0)	−233.9 (−491.9, 24.2)	59.4% (−87.0%, −31.7%)
2/1/2011	Everolimus[b] (non-first-competitior[c])	−26.6 (−120.4, 67.1)	17.6 (−14.6, 49.9)	43.9 (−18.3, 106.1)	23.0% (−10.9%, 56.9%)
6/1/2011	Changed reimbursement criteria[d] (therapy line)	−5.5 (−97.3, 86.4)	−12.5 (−47.5, 22.6)	−55.3 (−226.9, 116.3)	−17.9% (−66.2%, 30.5%)
1/1/2012	Temsirolimus[b] (non-first-competitior[c])	−21.3 (−114.2, 71.6)	−3.2 (−18.8, 12.5)	−34.1 (−127.9, 59.7)	−11.7% (−43.2%, 19.9%)
8/1/2012	Pazopanib[b] (first-competitor[c])	−151.0* (−217.1, −84.9)	5.2 (−16.0, 26.4)	−130.1* (−215.3, −44.9)	−48.4%* (−69.6%, −27.1%)

CI, confidence interval.
[a]Comprehensive analysis model included endogenous and exogenous factors, with the dependent variable of sorafenib prescribing volume.
[b]Intervention classified as exogenous factor (drug competition).
[c]Relationship between sorafenib and the competitor drug.
[d]Intervention classified as endogenous factor (changed reimbursement criteria).
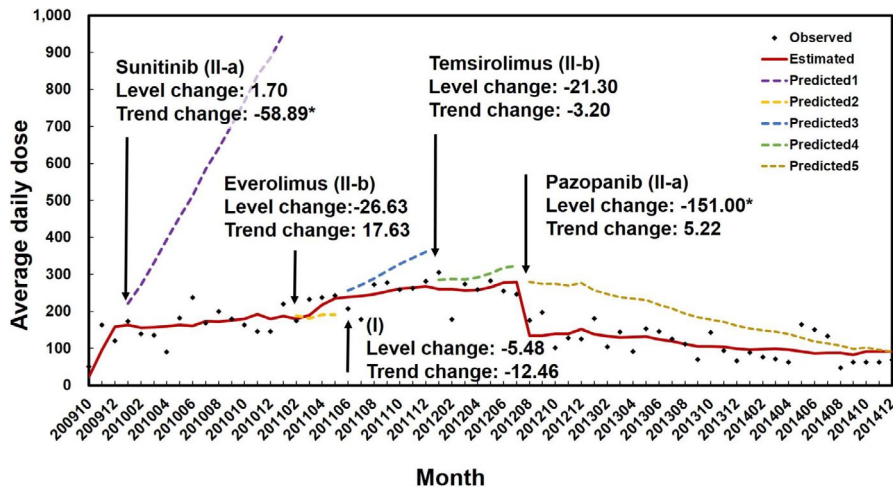*$P < 0.05$.

Figure 3 Trend in sorafenib prescribing volume before and after the interventions of changed reimbursement criteria (endogenous factors) and drug competition (exogenous factor). (I) Endogenous intervention factor (changed therapy line); (II-a) exogenous intervention factor (first-competitor); (II-b) Exogenous intervention factor (non-first-competitor). *$P < 0.05$.

secret. Nevertheless, we suppose that all studied drugs were subject to such agreements, because most innovative oncology drugs incur large budgetary impacts on the Taiwan NHI system. Finally, our analysis pertained only to oncology drugs specifically focused on mRCC in exogenous factor analysis, where more new drugs were reimbursed, and only on sorafenib in the comprehensive analysis. Therefore, the results cannot be generalized to other disease areas, therapeutic classes, or drugs. Notwithstanding these limitations, our study results provides important information about the utilization of innovative oncology drugs and, thus, serves as a useful model for future research focusing on other therapeutic classes or other drugs.

Implications
Our findings have several important implications. First, multiple factors influence drug utilization after innovative oncology drugs surmount the hurdle of reimbursement. As managing

drug utilization and controlling pharmaceutical expenditure is crucial for payers, they must pay due attention to evaluating post-reimbursement drug use, rather than focus exclusively on reimbursement decision making. Second, payers should take greater care in setting the initial price for a new drug. It is very likely that the indication of an innovative oncology drug will expand many times after initial reimbursement and the initial price might be incommensurate with the value of new indications. Third, having demonstrated that national reimbursement criteria play an important role in influencing drug utilization in oncology, there is a need to further investigate the effects of national drug utilization management strategies in other disease areas. Furthermore, different utilization management strategies in the national reimbursement criteria exerted different effects on prescribing volume in oncology. Understanding the effects of these strategies is important and such evidence will inform future decision making by payers. Fourth, we found that introduction of a new

drug influenced the prescribing volume of first-competitors and non-first-competitors; in addition, that usage volume of an existing earlier-line drug may increase upon entry of a new later-line treatment. Given the complicated and unpredictable effects of drug competition, it is prudent for payers forecasting the market share to consider a therapeutic class as a unit, rather than focus on single drugs. Finally, multiple factors significantly affect post-reimbursement oncology drug utilization. To improve drug utilization management and to empirical evidence for future decision making, policy-makers should evaluate such utilization regularly and consider the comprehensive effects of both endogenous and exogenous factors.

CONCLUSIONS

As the market for innovative oncology drugs grows, it is important for payers to determine which to reimburse, and to monitor their post-reimbursement utilization. The prescribing volume of innovative oncology drugs changes dynamically after they become reimbursed, and is influenced by both endogenous factors (changed national reimbursement criteria) and exogenous factors (competition). Our findings about the effects of national reimbursement criteria and drug competition may conduce to developing sound oncology drug utilization management strategies and benefit future decision making.

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