

ORIGINAL ARTICLE

Direct medical cost of non-small cell lung cancer patients treated with targeted therapy: A cross-sectional study in Vietnam

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ABSTRACT

Targeted therapy for the Epidermal Growth Factor Receptor (EGFR-targeted therapy) prolongs survival in patients with advanced stage (IV) non-small cell lung cancer (NSCLC), but its cost is slightly higher. Cost estimation and analysis of related factors are needed to reduce the economic burden for NSCLC patients and their households. We conducted a cross-sectional study from October 2022 to December 2023 at the Vietnam National Cancer Hospital. The characteristics and costs associated with 310 NSCLC patients were collected from medical records, medical bills, and patient interviews. The study utilized a social perspective and the bottom-up method. All costs have been adjusted for the Consumer Price Index (CPI) and standardized to 2023 USD. The mean total direct medical cost for 310 NSCLC patients was $\$839.7 \pm 486.4$ (Mean $\pm$ SD) per month, with EGFR-targeted therapy costs of $\$755.6 \pm 471.0$ per month, accounting for 90.0% of the total cost. In households with average or higher economic status, patients had higher costs for EGFR-targeted therapy than those in poor or near-poor households ($\$780.8$ and $\$480.2$ per month, respectively; $p = 0.001$). Compared with other individuals, NSCLC patients with higher education levels, residing in urban areas, having stable jobs, and average or higher household economic status had higher direct medical costs. However, these costs tended to decrease when the duration of illness increased, with $p < 0.05$ for each group. Direct medical costs are a significant burden for NSCLC patients living in poor or near-poor households, as well as for low-income or unemployed patients.

Keywords:

Non-small cell lung cancer, EGFR, targeted therapy, direct medical cost, cost-effectiveness.

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INTRODUCTION

Lung cancer is the most common cancer in the world, with 2.5 million new cases annually, accounting for 12.4% of all new cancer cases in 2022. The number of lung cancer cases is predicted to continue to increase and could reach 35 million by 2050.¹ Non-small cell lung cancer (NSCLC) accounts for approximately 85% of all lung cancer cases.^{2,3} In Southeast Asia, the incidence of lung cancer is the third highest, but it causes 166,260 deaths annually (10.9%), ranking first among cancers.⁴ The cause may be that patients with NSCLC are often diagnosed with stage IIIB or IV disease,^{3,5,6} leading to a poor prognosis with a low overall 5-year survival rate of only 17.4%.^{5,6}

In Vietnam, the incidence and mortality rates of lung cancer have ranked second since 2012.⁷ More than 80% of lung cancer patients have NSCLC, with 64.0% having EGFR mutations.⁸ Up to 89% of lung cancer patients are already in stage IIIB or IV when detected,⁹ and only 14.8% of patients can survive after 5 years of treatment,⁷ EGFR-targeted therapy is often prescribed for NSCLC patients who have EGFR mutation-positive and advanced stage (IV).^{5,10,11}

According to a 2014 study in Vietnam, the social cost for NSCLC treatment exceeded 3.5 trillion VND (150 million USD). Drug costs accounted for 73.9% (2.6 trillion VND), nearly three times higher than other medical services (900 billion VND).^{9,12} The high costs of cancer treatment contribute to 68% of households with lung cancer patients facing catastrophic medical expenses.¹³ and 37.4% of households falling into poverty.^{14,15} Some studies have shown that patients facing financial difficulties may try to cut treatment costs by lowering doses or skipping treatments,^{16–20} which can result in worsened symptoms and decreased survival time.^{16,21,22} In Vietnam, only a few studies have been conducted on patients with

advanced stage NSCLC and EGFR mutations. However, these studies have primarily focused on treatment methods.^{10,11} Therefore, we conducted this study to estimate direct medical costs, analyze factors related to patients, and assess how differences in household economic status affect direct medical costs among NSCLC patients.

METHODS

Study design

We conducted a cross-sectional study to collect data on the demographic characteristics and direct medical costs of NSCLC patients.

Study population

NSCLC patients received targeted therapy at the Vietnam National Cancer Hospital in Tan Trieu, specifically in the Department of Medical Oncology 1 and Medical Oncology 2, in Hanoi, Vietnam between October 2022 and December 2023. Patients were eligible for inclusion in this study if they met the following criteria: (1) were 18 years of age or older; (2) had a confirmed diagnosis of stage IV EGFR mutation-positive NSCLC through PCR tests, a histology or cytology results, and medical records; and (3) had initiated first-line targeted therapy at least one month prior to the start date of the study, October 1, 2022. The first month was excluded to accommodate dosage adjustments and medications that may not accurately reflect the patient's actual costs. Therefore, patient data were collected starting from the second month; (4) were able to communicate in Vietnamese during interviews; and (5) agreed to participate in the study by signing the consent form titled "Application for Volunteer Research".

Patients excluded from the study were those currently undergoing treatment for other acute illnesses, as well as those diagnosed with or suspected of being in advanced stages of the disease.

Direct medical costs estimate

Cost assessment perspective: In this study, direct medical costs were paid by patients and health insurance agencies. Therefore, we evaluated these costs from the perspectives of both patients and health insurance agencies.

Cost approach method: The bottom-up method, also known as the microcosting method, was used to estimate the costs of components identified in medical records and medical bills within one month of the patient interview.

The components of direct medical costs (five types) include collecting the unit price from medical bills and the quantity of each component cost type:

(1) Diagnostic imaging costs (DICs) include X-rays, CT scans, and ultrasounds.

(2) Laboratory test costs (LTCs) include blood counts, blood chemistry tests, urine tests, immunoassays, PCR tests, etc.

(3) EGFR-targeted therapy costs (ETCs) include those associated with targeted drugs such as erlotinib, gefitinib, afatinib, and osimertinib.

(4) Other drug costs (ODCs) include those associated with contrast agents, antidiarrheal drugs, topical medications, drugs used to treat elevated liver enzymes, pain relievers, sleeping pills, etc.

(5) Other service costs (OSCs) include hospital beds, pleural punctures, and medical consumables (cotton, gloves, gauze, needles, etc.).

The direct medical costs are calculated by multiplying the unit price and quantity of each type of cost component.

The total direct medical cost (TDMC) was calculated as follows:

$$\text{TDMC} = \text{DICs} + \text{LTCs} + \text{ETCs} + \text{ODCs} + \text{OSCs}$$

Cost adjustment and currency conversion

All costs have been adjusted for the Consumer Price Index (CPI)²³ and

estimated in 2023 VND. The costs were then converted to 2023 USD dollars the exchange rate of 1 USD = 23,993 VND. We relied on the foreign exchange rate announcement made by the Ministry of Finance of Vietnam in December 2023 (Reference number: 6885/TB-KBNN; dated: November 30, 2023).

Data collection method

The data collected for the study consisted of three main parts: (i) sociodemographic characteristics, (ii) clinical characteristics, and (iii) the components of direct medical costs.

(i) The patients' sociodemographic characteristics (age, sex, place of residence, education level, occupation, frequency of hospital visits, etc.) were collected through medical records and patient interviews.

(ii) Clinical characteristics of patients (type of mutation, stage of illness, duration of illness, treatment regimen, disease status (stable or progressive), and side effects) were collected from hospital medical records.

(iii) The components of direct medical costs (laboratory tests, diagnostic imaging, EGFR-targeted therapy costs, etc.) were collected through medical records and medical bills.

Statistical Analyses

All collected data were entered, cleaned, and coded in Excel version 2019 and analyzed via SPSS version 26.0. Categorical variables such as age group, sex, education level, residence, occupation, duration of illness, and side effects are presented as frequencies and percentages. Pearson's chi-square test or Fisher's exact test was used to determine the difference between two categorical variables. Numeric variables, including direct medical and component costs, were analyzed via means, standard deviations, medians, minimums, and maximums. The Kolmogorov-Smirnov test and histogram

were used to assess the normal distribution of numeric variables. To compare cost differences among categorical variables (two groups, three groups, or more), the Mann–Whitney U and Kruskal–Wallis H tests were employed. A p-value of less than 0.05 was considered statistically significant.

RESULTS

General characteristics of the study population

A total of 310 patients were included in the study, with the majority being over 60 years old (51.6%), female (51.0%), living in rural areas (71.3%), having a secondary school education (49.0%), and working as farmers or

workers (44.2%). Most patients had been ill for 12 months or less (65.2%), with the majority experiencing side effects (66.5%). The mean monthly income of patients was \$117.20 per month, while their households had an average monthly income of \$473.00.

Patients with poor or near-poor household economic status were typically younger than 60 years old ($p = 0.003$), female ($p = 0.153$), residing in rural areas ($p = 0.012$), having a secondary school education ($p < 0.001$), working as farmers or workers ($p < 0.001$), and having an illness duration of 12 months or less ($p = 0.049$). Additionally, these patients experienced side effects ($p = 0.283$). The mean monthly income of patients and their households in poor or near-poor economic status was lower than that of those in average or higher economic status ($p < 0.001$) (**Table 1**).

Table 1. Demographic and clinical characteristics of the study population (n = 310)

Characteristics		Total n (%)	Patients' household economic status ^a n (%)		p value
			Poor or near- poor (n = 26)	Average or higher (n=284)	
Age groups (years)	> 60	160 (51.6%)	6 (1.9%)	154 (49.7%)	0.003**
	≤ 60	150 (48.4%)	20 (6.5%)	130 (41.9%)	
Gender	Female	158 (51.0%)	17 (5.5%)	141 (45.5%)	0.153
	Male	152 (49.0%)	9 (2.9%)	143 (46.1%)	
Residence	Urban	89 (28.7%)	2 (0.6%)	87 (28.1%)	0.012*
	Rural	221 (71.3%)	24 (7.7%)	197 (63.5%)	
Education level	Intermediate or higher	36 (11.6%)	0 (0.0%)	36 (11.6%)	<0.001***
	High school	102 (32.9%)	1 (0.3%)	101 (32.6%)	
	Secondary school	152 (49.0%)	23 (7.4%)	129 (41.6%)	
	Primary school or lower	20 (6.5%)	2 (0.6%)	18 (5.8%)	
Occupation	Farmer or Worker	137 (44.2%)	22 (7.1%)	115 (37.1%)	<0.001***
	Freelancers	34 (11.0%)	0 (0.0%)	34 (11.0%)	
	Employment or business	32 (10.3%)	2 (0.6%)	30 (9.7%)	
	Retired	89 (28.7%)	1 (0.3%)	88 (28.4%)	
	Unemployed since illness	18 (5.8%)	1 (0.3%)	17 (5.5%)	

Characteristics		Total n (%)	Patients' household economic status ^a n (%)		p value
			Poor or near- poor (n = 26)	Average or higher (n=284)	
Income per month^b (USD/month)	Patients	117.2 ± 211.9	8.6 ± 20.8	127.1 ± 218.6	<0.001***
	Patients' household	473.0 ± 444.8	198.3 ± 196.5	498.1 ± 452.8	
Duration of illness (months)	> 24	38 (12.3%)	6 (1.9%)	32 (10.3%)	0.049*
	13-24	70 (22.6%)	7 (2.3%)	63 (20.3%)	
	≤ 12	202 (65.2%)	13 (4.2%)	189 (61.0%)	
Side effects	Yes	206 (66.5%)	20 (6.5%)	186 (60.0%)	0.283
	No	104 (33.5%)	6 (1.9%)	98 (31.6%)	

p value: Pearson chi-square test or Fisher's exact test; * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

^aPoor or near-poor households have received certificates from local governments and members of these households have been given free health insurance cards.

^bMann-Whitney U test,

Direct medical costs of NSCLC patients treated with targeted therapy for 1 month

Direct medical costs of patients with NSCLC in one month

The average direct medical cost for non-small cell lung cancer patients was \$839.70 per month. Within this amount, the

cost of EGFR-targeted therapy was \$755.60 per month, representing the highest proportion at 90.0%. Other drugs accounted for 4.8%, diagnostic imaging for 4.3%, laboratory tests for 0.8%, and other services for 0.5% per month, with the lowest point at only 0.1% of the total direct medical cost per month (**Table 2**).

Table 2. The mean direct medical costs of patients with NSCLC in one month (n = 310)

Direct medical costs (USD/month)	Mean	SD	Median	Min	Max	Total costs (n = 310)	% of total costs
Laboratory test	7.1	2.6	7.6	0.0	17.6	2,199.8	0.8%
Diagnostic imaging	36.6	69.9	0.0	0.0	378.9	11,333.7	4.3%
EGFR-targeted therapy	755.6	471.0	710.7	102.4	1774.0	234,226.1	90.0%
Other drug	39.9	48.3	26.9	0.0	312.1	12,380.2	4.8%
Other service	0.5	2.4	0.0	0.0	17.3	152.5	0.1%
Total direct medical costs	839.7	486.4	791.7	102.4	1929.7	260,292.3	100.0%

SD: Standard deviation, Min: Minimum, Max: Maximum

The direct medical costs for patients living in average- or higher-income households were greater than those living in poor or near-poor households. Specifically, costs for laboratory tests, diagnostic imaging, other drugs, and other services were higher for the former group. However,

patients in average or higher households had costs for EGFR-targeted therapy (780.80 USD/month) that were nearly 1.6 times higher than those of patients living in poor or near poor households (480.20 USD/month) (**Table 3**).

Table 3. Monthly component costs and household economic status of the patients (n = 310)

Components of the direct medical cost (USD/ month)	Patients' household economic status ^a				p value
	Poor or near-poor (n = 26)		Average or higher (n = 284)		
	Mean	SD	Mean	SD	
Laboratory test	6.9	2.8	7.1	2.6	0.795 ^b
Diagnostic imaging	30.2	53.6	37.1	71.2	0.846 ^b
EGFR-targeted therapy	480.2	386.2	780.8	470.5	0.001^{b, **}
Other drug	27.7	26.1	41.1	49.8	0.431 ^b
Other service	0.0	0.0	0.5	2.5	0.248 ^b

SD: Standard deviation, ^bMann–Whitney U test, * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

^aPoor or near-poor households have received certificates from local governments and members of these households have been given free health insurance cards.

Factors influencing the monthly direct medical costs of patients with NSCLC

The mean total direct medical costs (USD/month) were higher in patients aged 60 years or younger, men, and patients experiencing side effects, but these differences were not statistically significant. Patients living in urban areas had higher total direct medical costs than patients living in rural areas (965.5 USD/month compared with 789.0 USD/month). Patients with intermediate or higher education levels and those with

employment or business status had higher total direct medical costs than other subjects. Moreover, patients living in average-income or higher household status had higher total direct medical costs than patients living in poor or near-poor households (866.60 USD/month compared with 545.00 USD/month). The total direct medical costs of patients with non-small cell lung cancer with a duration of illness of 12 months or less (873.60 USD/month) were greater than those of the other groups (**Table 4**).

Table 4. Monthly direct medical costs on the basis of patient characteristics (n = 310)

Variables		Total direct medical cost (USD/month)		p value
		Mean	SD	
Age groups (years)	> 60	822.3	498.6	0.321 ^b
	≤60	858.2	473.9	
Gender	Female	811.8	482.4	0.265 ^b
	Male	868.6	490.3	
Residence	Urban area	965.5	483.1	0.004^{b, **}
	Rural area	789.0	479.5	
	Intermediate or higher	1104.9	561.7	
Education level	High school	892.3	465.1	0.005^{c, **}
	Secondary school	743.6	460.0	
	Primary school or lower	823.8	460.7	

Variables	Total direct medical cost (USD/month)		p value
	Mean	SD	
Occupation	Farmer & Worker	718.1	0.001^{c, **}
	Freelancers	863.1	
	Employee or business	1061.1	
	Retired	931.5	
	Unemployed since illness	872.8	
Household economic status	Average or higher	866.6	0.001^{b, **}
	Poor or near poor	545.0	
Duration of illness (months)	≥ 25	639.2	0.021^{c, *}
	13-24	850.5	
	≤ 12	873.6	
Side effects	Yes	859.6	0.114 ^b
	No	800.2	

SD: Standard deviation, ^bMann–Whitney U test, ^cKruskal–Wallis H tests, * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$

DISCUSSION

Our research results indicated that the mean direct medical cost for non-small cell lung cancer patients was \$839.70 per month, which is 21.9 times lower than that reported in a study conducted in the United States (\$18,354 per month),²⁴ and also lower than that reported in another study conducted in the United States on lung cancer patients with brain metastases (\$6,366 per month) and without brain metastases (\$5,640 per month).²⁵ This difference may arise from variations in the characteristics of each country's health care system, treatment models, choice of unit costs, differences in research subjects' characteristics, and more. As a result, comparing research results between cost estimates often presents certain challenges.^{26,27} In our study, the treatment was mainly outpatient therapy with oral targeted drugs, without combining radiotherapy or chemotherapy or using other methods, and there were no inpatient treatment costs. Another crucial factor contributing to the difference in costs

between our study and the two previous studies was the disparity in exchange rates between the Vietnamese Dong (VND) and the US dollar. At the time of our study, the exchange rate was 1 USD = 23,993 VND. Consequently, the variance in costs between our study and the aforementioned studies is justified.

Among the cost components, targeted drug costs (\$755.60 per month) accounted for the highest proportion (90%) of total direct health care costs. This result is similar to the findings of some studies conducted in Europe (77.4%)²⁹ and the Netherlands (67.53%)³² while fairly different from others such as Turkey (29.0%),²⁸ Italy (35.0%),²⁸ South Korea (32.0%) and (53.0%),³¹ and China (39.8%).³³ In our study, patients were treated as outpatients because the targeted drug was taken orally, eliminating the need for hospitalization. Patients visited the hospital monthly for check-ups, and for clinicians to order re-examinations with diagnostic imaging and laboratory tests as needed. They received medication and scheduled follow-up visits until they

progressed, resulting in no inpatient treatments. Studies have shown that targeted drugs can cause side effects such as fatigue, dry skin, acne, hair loss, nail inflammation, diarrhea, increased liver enzymes, and stomatitis.^{34–36} Patients may feel helpless when faced with long-term symptoms caused by targeted anticancer medications.³⁷ If a patient reports experiencing side effects due to targeted drug treatment, doctors will prescribe supportive medication to improve the patient's quality of life. Therefore, the main cost components focus on the targeted drug and other necessary supportive medications.

EGFR-targeted therapy costs and total direct medical costs were lower in patients with poor or near-poor household economic status and/or living in rural areas than in patients with average or higher household economic status and/or living in cities. In Vietnam, the payment rate for health care services is determined by the type of health insurance card held by the individual. For instance, members of poor households receive full coverage. The decision regarding EGFR-targeted therapy and treatment regimen is left to the patient. It is important to note that first-generation EGFR-targeted therapies such as Erlotinib and Gefitinib,³⁸ as well as second-generation therapies, like Afatinib³⁸ are only partially covered by health insurance at a rate of 50%. Patients from poor households receive 50% coverage, while those from near-poor households receive 47.5%. However, for third-generation EGFR-targeted therapy, Osimertinib,³⁸ patients are required to pay 100% out of pocket. Our findings showed that the average monthly cost for EGFR-targeted therapy was \$755.60, which was 6.4 times higher than the average income of the patient (\$117.20 per month) and 1.6 times higher than the income of the patient's family (\$473.00 per month). For patients not covered by health insurance, the cost for EGFR-targeted therapy was 87.9 times

higher than the average monthly income of patients living in poor household status (\$8.60 per month). Some studies have indicated that patients facing financial difficulties may try to cut treatment costs by lowering doses or skipping treatments,^{16–20} which can result in worsening symptoms and decreased survival time.^{16,21,22} Therefore, supporting health insurance coverage for EGFR-targeted therapy drugs is of great significance because it provides patients with the opportunity to receive treatment and prolong their lives.

A study conducted in China also revealed that patients with higher family income and better housing had higher costs.³³ According to a study in England, lung cancer patients with poor economic conditions and/or living in impoverished areas were less likely to receive chemotherapy than those with better economic conditions (OR: 0.39; 95% CI: 0.16–0.96),³⁹ and those residing in affluent areas (OR = 0.73).⁴⁰ This finding may explain why patients in rural areas and/or those with poor or near-poor conditions opt for lower-cost treatments or reduce related costs more than patients in cities do and/or who have better economic conditions. Among the component costs, the cost of EGFR-targeted therapy is the highest, suggesting that patients may choose more affordable drugs on the basis of their household's economic conditions.

Patients with a higher education level incur higher direct medical costs, and those with stable jobs (such as employment, business, or retired individuals) have higher costs than other subjects (unemployed, farmers, workers, or freelancers). This finding is consistent with a study conducted in China.³³ Additionally, education, occupation and income are interrelated at low to medium levels.⁴¹ A higher education level can help individuals better understand health and take better care of themselves.⁴² Education level and income also play a role in the utilization of lung cancer screening services to reduce mortality from

NSCLC.⁴³ This may explain why patients with a higher education level, stable jobs, and higher income exhibit better health care behaviors, leading to higher treatment costs.

Direct medical costs tended to decrease with the duration of illness for non-small cell lung cancer patients. This trend may be explained by the disease process leading to reduced employment, fewer workdays, decreased work capacity and efficiency, lower income, and the risk of financial impact for cancer survivors post-treatment. Additionally, cancer patients face risks such as personal loans or mortgages, higher out-of-pocket expenses, household bills, limited health insurance status, and lower quality of life.⁴⁴

STRENGTHS AND LIMITATIONS

Our study on direct medical costs in patients with stage IV EGFR-mutant non-small cell lung cancer treated with targeted therapy is one of the first conducted in Vietnam. This study is also part of our follow-up study on the cost-effectiveness of targeted drugs in Vietnam. However, our study has several limitations, such as (1) being conducted only at a leading cancer treatment hospital in Vietnam and (2) having a sample size of 310 patients with non-small cell lung cancer, which may not be representative enough to be generalized to the whole country. Additionally, (3) we only collected direct medical costs, which do not reflect all the costs patients have to pay, (4) this study is only a cross-sectional study over a period of one month, so it does not fully reflect the total costs patients have to pay from the time of illness to death. These limitations may also affect the results of our study. Furthermore, our study focused on stage IV NSCLC patients with EGFR mutations. Therefore, this study was unable to evaluate all costs associated with

other types of mutations or different stages of NSCLC patients.

RECOMMENDATIONS

The government needs to implement policies that support patients from poor or near-poor households, as they are the most vulnerable. Increasing the level of support from health insurance and providing free health insurance cards to members of poor households, low-income patients, those unemployed due to illness, and people living in rural areas are essential to reduce direct medical costs that could potentially push them into poverty. Our findings suggest a future direction for research focused on the factors associated with the decrease in direct medical costs for NSCLC patients over time. This also raises questions about how these factors may affect treatment outcomes as well as increases in progression and mortality.

AUTHOR CONTRIBUTIONS

Conceptualization and methodology: Chinh Van Nguyen, Hoa Thi Thai Nguyen, Tram Nguyen Nguyet Luu, Linh Khanh Dao, Huong Thi Thanh Tran, Kiet Tuan Pham Huy. Data curation and investigation: Chinh Van Nguyen. Formal analysis and software: Chinh Van Nguyen, Kiet Tuan Pham Huy, Huong Thi Thanh Tran. Supervision: Kiet Tuan Pham Huy, Huong Thi Thanh Tran, Hoa Thi Thai Nguyen, Linh Khanh Dao, Tram Nguyen Nguyet Luu. Validation and visualization: Chinh Van Nguyen, Kiet Tuan Pham Huy, Huong Thi Thanh Tran. Writing – original draft: Chinh Van Nguyen, Kiet Tuan Pham Huy, Huong Thi Thanh Tran. Writing – review & editing: Chinh Van Nguyen, Hoa Thi Thai Nguyen, Tram Nguyen Nguyet Luu, Linh Khanh Dao, Huong Thi Thanh Tran, Kiet Tuan Pham Huy.

ETHICAL CONSIDERATION

Our study was approved by the board of directors of Vietnam National Cancer Hospital (Reference number: 12a/TTr-VUT, dated October 07, 2022). We also obtained research ethics certificates from the Hanoi Medical University Institutional Ethical Review Board (HMU IRB) with reference numbers: 666/GCN-HĐNCYSH-DHYHN, on August 30, 2022, and 974/GCN-HĐNCYH-DHYHN, on August 06, 2023.

All research subjects provided written informed consent to participate in this study. Patient information, medical records, and cost data were collected and managed following correct procedures, kept strictly confidential, and used solely for research purposes.

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CONFLICT OF INTEREST

We declare that we have no conflicts of interest regarding this article.

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