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Hospital-by-hospital carbapenem use in Japan: a nationwide ecological study

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SUMMARY

Background: The Japanese healthcare system has been based on universal health coverage since 1961. Nationwide antimicrobial use on a hospital-by-hospital basis has not previously been recorded.

Objectives: To determine the nationwide distribution of carbapenem use on a hospital-by-hospital basis and to build predictive models using available hospital data from Japan.

Methods: An ecological study was conducted using open data released from the Government of Japan. The distribution of days of therapy with carbapenem (per 1000 patient-days) was analysed and predictive models built. The top 1% heavy users by crude distribution and observed-per-predicted ratio distribution were listed and compared. The analysis was conducted in three subcategories stratified by hospital characteristics (tertiary, secondary acute care, and fee-for-service) and among patients in two age groups (16–65 and >65 years).

Findings: The median days of therapy in the group aged 16–65 years were 7.24 for tertiary hospitals, 3.28 for secondary acute care hospitals, and 1.42 for fee-for-service hospitals. The median days of therapy of the group aged >65 years were 17.28 for tertiary hospitals, 14.43 for secondary acute care hospitals, and 8.21 for fee-for-service hospitals. For multivariable linear regression analyses, each model selected a different combination of covariates from the potential predictors based on hospital characteristics.

Conclusion: Because a single predictive model was not appropriate for all hospitals, tailored models are needed to identify hospitals that are heavy users of carbapenem. These findings may serve as a reference to support further research on antibiotic use in healthcare and aid future policies.

Introduction

The healthcare system of Japan has been based on universal health coverage since 1961 [1]. In principle, 30% of healthcare costs are paid out-of-pocket and the remaining 70% is paid by insurance. It is not a single-payer system, but all payments are operated according to a single tariff set by the government. There are many additional payment schemes designed to incentivize hospitals to improve the quality of practice. These schemes include some requirements for hospitals to receive payments but the revenue of hospitals is not earmarked. Pay for performance (P4P) has not been adopted in Japan at present, and there is no punitive arrangement with regard to the payments, such as denial of additional payments to hospitals with a high prescription rate of a particular class of antibiotics.

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In March 2018, the Government of Japan released data on carbapenem days of therapy (DOT) from 3501 hospitals on a hospital-by-hospital basis [2]. These hospitals submitted government Diagnosis Procedure Combination (DPC) data containing all the clinical information required for the payment for services. DPC is a type of diagnosis-related group reimbursement system implemented in Japan and covers >80% of all acute care hospitals [3,4]. There are ~8500 hospitals in Japan; therefore, these data cover >40% of hospitals nationwide [5]. This is the first official release of government data detailing antibiotic use in a clinical setting rather than antibiotic purchase [6,7]. Some countries collect data related to hospital or regional unit distribution of antibiotic use, resistance, and infection rate, and use these for adjusting payments from public funds as P4P [8,9]. To the best of our knowledge, there are no reports in the literature that have described nationwide antimicrobial use on a hospital-by-hospital basis [10,11]. Using national data, this study attempted to evaluate three factors: distribution and density of carbapenem use; whether hospital characteristics affect carbapenem use; and whether predictive models will be useful in identifying hospitals that overuse carbapenems. Regression analysis was conducted to predict DOT with carbapenem and to calculate observed-per-predicted ratios to explore the distributions.

Methods

Data

Government data from the DPC survey of patients discharged in the 2016 fiscal year (April 2016 to March 2017) were used in this study. A total of 3501 hospitals submitted DPC format data to the government during this period. The data included DOT (per 1000 patient-days) for all intravenous carbapenems marketed in Japan (imipenem, meropenem, biapenem, doripenem, and panipenem). According to the original data set, DOT for each hospital was calculated for patients belonging to three age groups: <15, 16–65, and >65 years. However, patients in the group aged <15 years were excluded from this study, because we considered that the optimal duration of antibiotic therapy is not consistent across neonates and adolescents. The data were collected from regular wards, including intensive care units (with a nurse:patient ratio of at least 1:10); less intensive wards, such as long-term care units, were not included. The original data sets excluded data with overlapped submission, hospitalizations lasting up to one day, out-of-hospital-stay days greater than hospitalized days, incorrect entry of admission day or date of birth, death within 24 h of admission, organ transplant including bone marrow transplantation, no insurance payment (full out-of-pocket payment), and participation in therapeutic trial. Consistent with Japan's policy, approval by the institutional review board of Osaka University was not required because the data used in this study were public access data provided by the government and had no patient identifiers [12].

The 3501 hospitals were stratified based on the reimbursement scheme: class I DPC (all university hospitals) ($N = 81$), class II DPC ($N = 140$), class III DPC ($N = 1445$), DPC-preparing hospitals ($N = 276$), and fee-for-service hospitals ($N = 1559$). For the analyses, three subsets of hospital characteristics were created using the aforementioned reimbursement categories: 'tertiary hospitals' (classes I and II DPC), 'secondary acute care hospitals' (class III DPC), and 'fee-for-service hospitals' (DPC-preparing and fee-for-service). Hospitals with <10 cases of carbapenem use in the study period were designated as blank in the original data set; these hospitals were classified as having missing values and were excluded from the analysis.

Study design and statistical analysis

An ecological study was conducted using data from 3501 hospitals in Japan. DOT (per 1000 patient-days) were summarized by the age groups 16–65 and >65 years according to each subset and hospitals with crude parameters >99th percentile were identified.

In simple analyses, DOT were used for tertiary hospitals as outcome variables. However, the natural logarithm of DOT was used for secondary acute care hospitals and fee-for-service hospitals, where the distributions were right-skewed. Simple linear regression analyses were performed to test the effect of chemotherapy, radiation therapy, ambulance admission, and general anaesthesia on the outcomes. Data pertaining to these potential confounding factors were released by the government [2]. Chemotherapy, radiation therapy, and general anaesthesia represented the proportions of patients who received these medical services during hospitalization, among the total number of patients who were discharged from each hospital during the study period. Ambulance admission indicates the proportion of patients who were admitted from ambulances.

A multiple linear regression model was constructed to predict DOT with carbapenem. Chemotherapy, radiation therapy, ambulance admission, and general anaesthesia were evaluated as independent variables. A backward elimination algorithm was used, set at $P < 0.10$, to select covariates. For dependent variables in the model, DOT or its natural logarithm was used, as applicable. Using the predictive model, DOT were predicted for each hospital and the ratio of observed DOT per predicted DOT was calculated.

Distributions of the observed-per-predicted ratios were examined and hospitals with ratios >99th percentile identified. The 'top 1% heavy users' listed by the crude distribution and the observed-per-predicted ratio distribution were compared. The concordance rate of the lists was calculated. All statistical analyses were performed using Stata 14 statistical software (Stata Corp., College Station, TX, USA) and $P < 0.05$ was considered statistically significant, except for regression model selection as previously mentioned.

Results

There were no missing values for tertiary hospitals. For secondary acute care hospitals, there were 46 missing values (3.2%) in the group aged 16–65 years and 25 missing values (1.7%) in the group aged >65 years. There were 695 missing values (37.9%) in the group aged 16–65 and 344 missing values (18.7%) in the group aged >65 years for fee-for-service hospitals. The only explanation for missing values was that <10 cases of carbapenem use were recorded at one hospital during the study period.

Days-of-therapy distributions are presented in Figure 1 and 2, and Table I. The median DOT was higher in tertiary hospitals

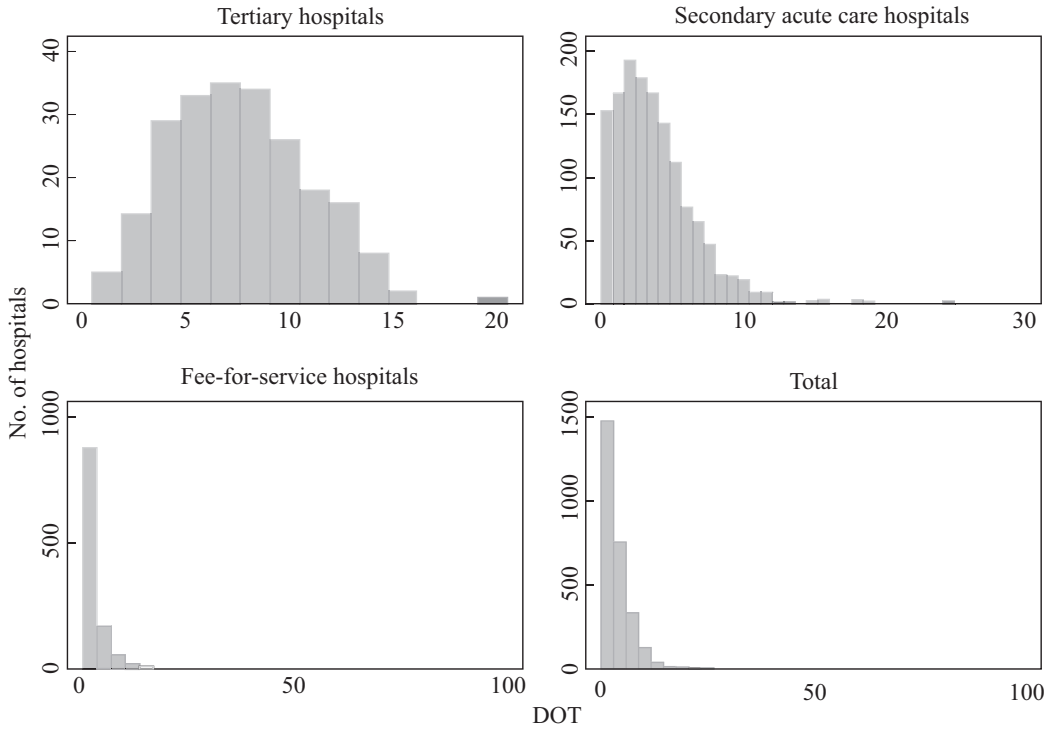

Figure 1. Distribution of days of therapy according to hospital characteristics (age 16–65 years).

than in secondary acute care hospitals and fee-for-service hospitals. However, both secondary acute care hospitals and fee-for-service hospitals had wider ranges of DOT with carbapenem than did tertiary hospitals, which typically dealt with greater clusters of patients. Outliers were observed among fee-for-service hospitals.

The results of the simple analyses are presented in Table II. For the group aged 16–65 years, all factors, excluding radiation therapy in fee-for-service hospitals, yielded statistically significant results (chemotherapy, ambulance admission, and general anaesthesia). The results varied when analysing the effect of ambulance admission; it was a significant negative

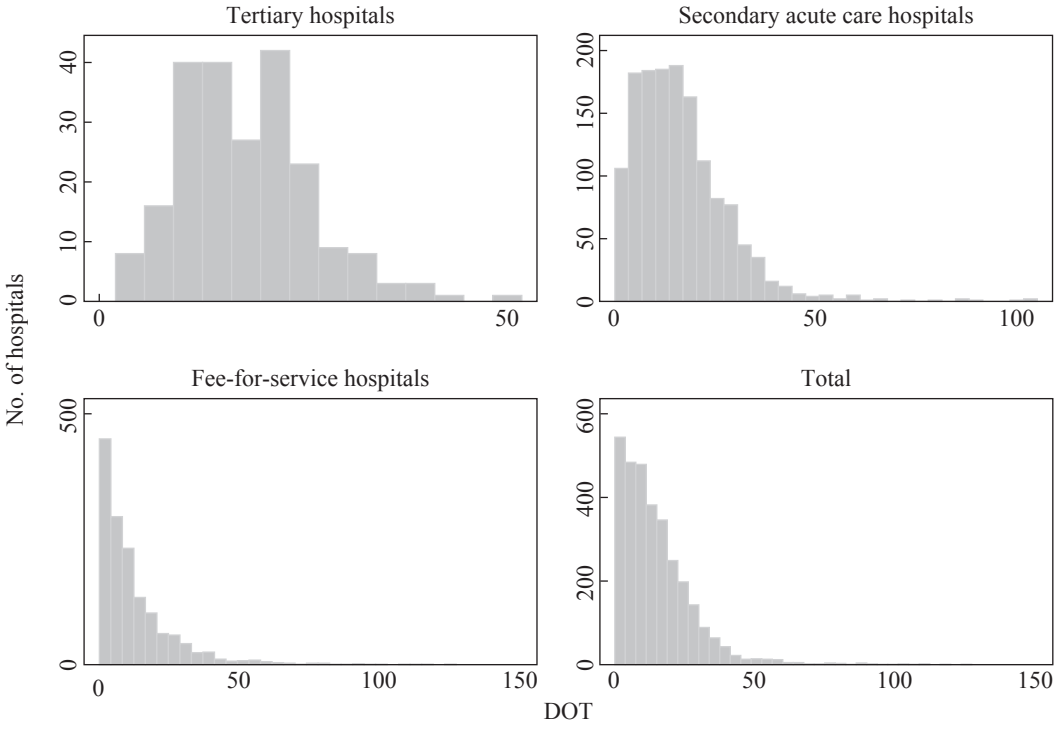

Figure 2. Distribution of days of therapy according to hospital characteristics (age >65 years).

Table I
Summary of days of therapy

Age group	Hospital type	Days of therapy			
		Median	95th percentile	99th percentile	Longest
16–65 years	Tertiary ($N = 221$)	7.24	13.31	15.21	20.58
	Secondary acute care ($N = 1399$)	3.28	8.94	13.18	24.95
	Fee-for-service ($N = 1140$)	1.42	8.33	16.18	99.88
	Total ($N = 2760$)	2.68	9.85	15.13	99.88
>65 years	Tertiary ($N = 221$)	17.28	32.71	40.21	51.68
	Secondary acute care ($N = 1420$)	14.43	36.11	59.19	104.60
	Fee-for-service ($N = 1491$)	8.21	39.26	76.73	126.72
	Total ($N = 3132$)	11.76	36.98	64.64	126.72

predictor for tertiary hospitals and secondary acute care hospitals but a positive predictor for fee-for-service hospitals. However, the corresponding adjusted R^2 values were 0.04, 0.01, and <0.01, respectively. Except for ambulance admission, all other significant predictors increased DOT by varying increments in the group aged 16–65 years. For the group aged >65 years, radiation therapy, ambulance admission, and general anaesthesia were significant predictors of DOT with carbapenem for tertiary hospitals; chemotherapy and general anaesthesia were significant predictors for secondary acute care hospitals; and chemotherapy, ambulance admission, and general anaesthesia were significant predictors for fee-for-service hospitals, although the adjusted R^2 values were up to 0.05. Contradictory results were observed between the age groups with respect to the effect of radiation therapy and ambulance admission in tertiary hospitals. In addition, the direction of the effect of general anaesthesia in tertiary hospitals and secondary acute care hospitals differed according to age group.

Multivariable factors are presented in Table III. For the group aged 16–65 years, radiation therapy was the only significant factor for tertiary hospitals; chemotherapy and

Table II
Single regression coefficients, according to age groups and hospital characteristics[a]

Age group, therapy/procedure	Regression coefficient		
	Tertiary hospitals	Secondary acute care hospitals (based on natural logarithm)	Fee-for-service hospitals (based on natural logarithm)
16–65 years			
Chemotherapy	14.31	4.80	5.45
Adjusted R^2	0.04	0.10	0.08
P-value	<0.01	<0.01	<0.01
Radiation therapy	58.73	4.27	2.32
Adjusted R^2	0.05	<0.01	<0.01
P-value	<0.01	<0.01	0.20
Ambulance admission	−10.98	−1.12	0.92
Adjusted R^2	0.04	0.01	<0.01
P-value	<0.01	<0.01	<0.01
General anaesthesia	10.21	0.93	0.28
Adjusted R^2	0.01	<0.01	<0.01
P-value	0.046	<0.01	0.29
>65 years			
Chemotherapy	−20.61	2.60	3.92
Adjusted R^2	0.01	0.03	0.03
P-value	0.052	<0.01	<0.01
Radiation therapy	−130.32	−0.06	−1.10
Adjusted R^2	0.04	<0.01	<0.01
P-value	<0.01	0.96	0.52
Ambulance admission	29.18	0.21	1.00
Adjusted R^2	0.05	<0.01	<0.01
P-value	<0.01	0.43	<0.01
General anaesthesia	−30.11	−1.64	−1.34
Adjusted R^2	0.02	0.03	0.02
P-value	0.01	<0.01	<0.01

[a] How much dependent variables would increase when each independent variable is increased by 100%.

Table III
Multivariable factors for days of therapy

Age group, hospital type, therapy/procedure	Coefficient (95% CI)	Adjusted R^2
16–65 years		
Tertiary hospitals		
Radiation therapy	58.73 (24.84–92.63)	0.05
Secondary acute care hospitals (based on natural logarithm)		
Chemotherapy	4.71 (3.95–5.47)	0.10
General anaesthesia	0.64 (0.14–1.13)	
Fee-for-service hospitals (based on natural logarithm)		
Chemotherapy	5.86 (4.80–6.93)	0.10
Ambulance admission	1.49 (0.86–2.13)	
>65 years		
Tertiary hospitals		
Ambulance admission	29.18 (13.19 to −45.17)	0.05
Secondary acute care hospitals (based on natural logarithm)		
Chemotherapy	3.13 (2.34–3.92)	0.07
Ambulance admission	0.76 (0.21–1.30)	
General anaesthesia	−1.64 (−2.09 to −1.18)	
Fee-for-service hospitals (based on natural logarithm)		
Chemotherapy	4.61 (3.55–5.67)	0.07
Radiation therapy	−3.43 (−6.73 to 0.14)	
Ambulance admission	1.34 (0.77–1.91)	
General anaesthesia	−1.49 (−1.94 to −1.03)	

CI, confidence interval.

general anaesthesia were significant predictors for secondary acute care hospitals; and chemotherapy and ambulance admission were significant predictors for fee-for-service hospitals. The highest adjusted R^2 value was 0.10 (secondary acute care hospitals and fee-for-service hospitals). For the group aged >65 years, ambulance admission was the only significant predictor for tertiary hospitals; chemotherapy, ambulance admission, and general anaesthesia were significant predictors for secondary acute care hospitals; and chemotherapy, radiation therapy, ambulance admission, and general anaesthesia were all significant predictors for fee-for-service hospitals. General anaesthesia in secondary acute care hospitals and fee-for-service hospitals was a negative predictor of DOT with a carbapenem. In addition, radiation therapy was a negative predictor for fee-for-service hospitals. The direction of the effect of general anaesthesia in secondary acute care hospitals differed between both age groups, similar to that in the simple analysis.

The concordance rates, which reflect the comparison of the two listing methods (observed value basis and observed-per-predicted ratio basis), are presented in Table IV. Tertiary hospitals on the lists were identical for the group aged >65 years. However, hospitals belonging to other categories varied depending on the listing methods, and the concordance rate ranged from 33% to 100%.

Table IV
Days of therapy concordance rates of the top 1% heavy users

Age group	Hospital type	Concordance rate
16–65 years	Tertiary	33% (1/3)
	Secondary acute care	71% (10/14)
	Fee-for-service	67% (8/12)
>65 years	Tertiary	100% (3/3)
	Secondary acute care	80% (12/15)
	Fee-for-service	73% (11/15)

Discussion

To the best of our knowledge, this is the first nationwide study of carbapenem use on a hospital-by-hospital basis. Although the NHS England released data on antibiotic prescriptions in primary and secondary care centres per population on a regional basis, there have been no nationwide studies on hospital-by-hospital antibiotic use involving most acute care hospitals in any country [13]. Unlike England, Japan does not have 'regions' as administrative units for healthcare delivery. People in Japan can choose hospitals regardless of which part of the country they live in, making any regional data rather arbitrary. Instead, we used hospital-by-hospital data stratified by DPC class. Regional data such as Public Health England data may be more appropriate for England considering its healthcare system. However, from the international perspective, many countries, like Japan, do not set administrative boundaries for healthcare deliveries. Fridkin *et al.* reported the distribution of DOT with some antibiotics, such as quinolones, third- and fourth-generation cephalosporins, and vancomycin on a hospital-by-hospital basis [14]. However, the data were collected from only 19 hospitals in the USA. In our ecological study involving 3501 hospitals, we determined predictive regression models for DOT of each age and hospital characteristics stratum, using indicators of chemotherapy, radiation therapy, ambulance admission, and general anaesthesia. To build the predictive models, stratification by hospital characteristics and age groups was important. The selected covariates were different based on the hospital's characteristics. Furthermore, even with the same covariates, the coefficient could be significantly negative or positive depending on the specific category. Thus, it appeared prudent to determine a single model to predict DOT for all hospitals and all age groups. Otherwise, an extremely complicated model with many effect modifications would be needed.

The DOT values in tertiary hospitals were normally distributed, implying that these hospitals were homogeneous in terms of carbapenem use. Out of 221 tertiary hospitals, 81 were university hospitals (class I DPC) and 140 were class II DPC hospitals, which the government had designated equivalent to university hospitals. However, secondary acute care hospitals (class III DPC) and fee-for-service hospitals were more heterogeneous and larger (1445 and 1835, respectively) categories leading to distributions that were right-skewed.

Based on each distribution, we observed the top 1% heavy users. The hospitals listed may argue that the high density of carbapenem use should be excused due to patient conditions that were severe or susceptible to infection. Thus, observed-per-predicted ratios were calculated using predictive models to adjust for chemotherapy, radiation therapy, ambulance

admission, and general anaesthesia using available open data from government sources. The observed-per-predicted ratio is a statistic similar to the standardized infection ratio or the standardized mortality ratio, and it functions as an adjusted parameter [10,15]. On comparing the lists of observed and adjusted heavy users, some discrepancies were observed. The concordance rate was as low as 33%, which means that two-thirds of hospitals listed by crude distribution were replaced by others in the adjusted list. Thus, although the adjusted R^2 values were modest in the all predictive models, these values are still needed for fairness of listing the heavy users.

We believe that this study may help guide policies aimed at mitigating the overuse of antibiotics. The Government of Japan has launched a national action plan to address antibiotic resistance, with a target resistance rate of *Pseudomonas aeruginosa* to carbapenem of <10% by 2020 [16]. To reduce carbapenem use, the government may implement a policy that includes the denial of additional payments to hospitals with a high density of carbapenem use. However, for this type of potential policy, sufficient attention should be given to the fairness of hospital listings. Our study may provide insight for this purpose.

Another potential benefit of this study is to use its findings as a clinical indicator to provide the general public with information regarding antibiotic use. Although the government released crude data, it is almost impossible for the general public to comprehend and use this information when making decisions regarding the choice of hospital [17,18].

Our study has several limitations. First, the generalizability of the data to all hospitals in Japan should be considered. The total number of hospitals in Japan is ~8500, and our data account for only 40% of all hospitals [5]. However, most acute care hospitals are included in this study, since >80% are covered by the DPC reimbursement system ('tertiary hospitals' and 'secondary acute care hospitals' in our study). Furthermore, the remaining acute care hospitals were incentivized to submit their data and were included in the data set, even if they were not covered by the DPC reimbursement system ('fee-for-service hospitals').

Second, there may be concern regarding missing data. Data from hospitals with <10 cases of carbapenem use during the study period were left blank in the original data set. Although there were no missing data for tertiary hospitals and few instances of missing data for secondary acute care hospitals, a substantial number of fee-for-service hospitals (37.9% for the younger age group and 18.7% for the older age group) had missing data. This implies that some hospitals in the category of fee-for-service hospitals seldom used carbapenems. Therefore, missing values were excluded from our analyses, since our focus was on active hospital function for the treatment of infections.

Third, a limited number of variables were incorporated in this study. Although there is much information in the DPC database, the Minister of Labour, Health, and Welfare of Japan has disclosed a limited number of variables tied to the data of antimicrobial consumption by DPC hospitals.

Finally, we did not evaluate the appropriateness of carbapenem use on a case-by-case basis, since it was not feasible in this ecological study. If evaluated, we may have observed that high density of use was due to overtreatment in some hospitals ('excess' inappropriate use) or that low density of use was due to undertreatment in others (extreme 'access' limitation) [19]. However, considering some previous reports that a large proportion of antimicrobial use in healthcare settings was due to misuse or overuse, we propose that the bottom 99% is a large enough margin to evade type I error, where 'not-heavy-user' hospitals were listed [20,21].

In conclusion, this study elucidated the hospital-by-hospital patterns of carbapenem use in Japan. Although a single predictive model was not appropriate for all hospitals or age groups, we need tailored models for listing hospitals that are heavy users of carbapenems. These findings may serve as a reference to support further research on antibiotic use in healthcare and eventually inform policy development.

Conflict of interest statement

D. Morii reports receipt of personal fees from Daiichi-Sankyo for academic speeches. K. Tomono reports receipt of grants from Daiichi-Sankyo, Shionogi, and MSD, as well as personal fees from Meiji Seika. R. Kokado has no conflict of interest.

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