



# Utilization Patterns of Coagulation Factor Consumption for Patients with Hemophilia

Soo Ok Lee and Su-Yeon Yu

Health Insurance Review and Assessment Services,  
Seoul, Korea

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Address for Correspondence:  
Su-Yeon Yu, MS  
Health Insurance Review and Assessment Services,  
Seochopyeonghwa Building 11F, 22 Banpo-daero, Seocho-gu,  
Seoul 06716, Korea  
Tel: +82.2-2182-2600, Fax: +82.2-6710-5842  
E-mail: [suyeony@hiramail.net](mailto:suyeony@hiramail.net)

Hemophilia is a serious rare disease that requires continuous management and treatment for which the medicine is costly at the annual average of 100 million KRW for an individual. The aim of this study was to investigate trends in the utilization of coagulation factor (CF) used for hemophilia treatment using the National Health Insurance database from 2010 to 2013 in Korea and compare the utilization of CF with other countries. The consumption of CF per capita (IU) in Korea was not more than other countries with similar income to Korea. However, CF usage per patient IU was higher because the prevalence rate of hemophilia in Korea was lower than in other countries while the number of serious patients was much more. Therefore, it is difficult to say that the consumption of hemophilia medicine in Korea is higher than that in other countries. The consumption and cost of hemophilia medicine in Korea is likely to increase due to the increased utilization of expensive bypassing agents and the widespread use of prophylaxis for severe hemophilia. Even during the research period, it increased slightly and other countries show a similar trend. Thus, hemophilia patient management should accompany active monitoring on the health and cost outcomes of pharmaceutical treatment in the future. This study is expected to contribute to further insight into drug policies for other countries that face similar challenges with high price pharmaceuticals.

**Keywords:** Hemophilia; Coagulation Factor; Utilization; Cost

## INTRODUCTION

Hemophilia is a disease that causes bleeding by congenital deficiencies of coagulation factors, which is present in about 400,000 or 1 in 10,000 worldwide. The factor VIII (FVIII) deficiency and the factor IX (FIX) deficiency are the most common type of the disease, which are called hemophilia A and hemophilia B, respectively. Parts of hemophilia have inhibitors to coagulation factor. Though hemophilia patients have a good quality of life when treated adequately, they could reach disability or death following extreme pain and serious damage when appropriate treatment is not provided (1-5).

The National Health Insurance (NHI) system in Korea has listed hemophilia as a severe and rare disease and charges a lower copayment rate than other diseases. The Korea Hemophilia Foundation (KHF) supports hemophilia patients by sharing health care cost (6). The effort to improve the treatment environment of hemophilia patients has increased the average life expectancy from 27 yr in 1991 to 48 yr in 2010. Patients born after 1991 can expect an average lifespan of 76 yr, which has approached to that of normal persons (1,5,7,8).

Coagulation factor (CF) are expensive pharmaceuticals and take much financial resources from the NHI (6). In 2013, total hemophilia patients spent 170 million USD and a patient spent

90 thousand USD in order to be treated with CF for outpatient treatment. This indicates that the cost was very high compared to the average pharmaceutical cost per patient of 265 USD. In the United States, hemophilia patients insured through Medicaid spent 142,987 USD (median value of 46,737 USD) for annual health care costs. The patients prescribed with inhibitors spent 3.6 times more than those without inhibitors. The ratio of CF cost over the total health care cost of hemophilia patients was 64% for those with inhibitors and 86% for those without inhibitors (9). The median value of hemophilia A-related cost in the United States was 69,935 USD per patient annually (271,357 USD for those prescribed with inhibitors), and the variation of the total cost among patients was large (10). The cost to treat hemophilia has tended to increase. The total inpatient treatment cost in Taiwan between 2001 and 2010 has confirmed this tendency from the treatment records of 2,150 hemophilia patients (11). The utilization of FVIII, FIX, and bypassing agents increased by an average of 13.7%, 33.2%, and 34.2% per year, respectively (12).

CF needs to be managed not to be abused or wasted. CF also needs to be provided in a timely manner. A study on the utilization pattern of hemophilia treatment should be conducted. Therefore, this study reviews the utilization pattern of CF from the context of cost and utilization, and compares these indicators with

the reports from other countries. The study also suggests how the prescription efficiency of hemophilia treatment can be enhanced by reviewing other national healthcare systems.

## MATERIALS AND METHODS

Data were drawn from the National Health Insurance (NHI) claims database and provided by the Health Insurance Review and Assessments (HIRA). HIRA is an agency for the assessment of reimbursement claims under a single national healthcare system in Korea. NHI claims data included medical data (procedure codes), provider specialty, medical service data, and drug prescriptions (13).

Inclusion criteria were hemophilia patients receiving a CF as an inpatient or outpatient care treatment from 2010 to 2013, which is a FVIII product, FIX product, or bypassing agent (aPCC or rF-VIIa). Only claims including CF for hemophilia treatment (WHO ATC B02BD, blood coagulation factor) were included in this analysis. Individuals receiving at least one bypassing agent were defined as inhibitor patients and the others as non-inhibitor patients. Among non-inhibitor patients, those who were treated with a FVIII product and a FIX product are defined as hemophilia A and hemophilia B, respectively. Evaluation measures used were total CF cost and use (international units, IU), per-patient CF cost and IU, and per capita CF IU per year. Costs were measured in 2013 USD and are outlined. The nation's total population figures were obtained from the value estimated by Statistics Korea, the national statistical agency (14).

In addition, the Annual Global Survey (2012) of the World Federation of Hemophilia (WFH) was employed to compare the consumption of CF in Korea with that of other countries whose higher gross national income (GNI) is larger than 12,196 USD. The survey includes usage per capita of FVIII and FIX and the severity of patients by country (15). The data was summarized using descriptive statistics. SAS and Microsoft Excel 2007

were used for the analyses.

## RESULTS

The number of hemophilia patients prescribed with CF grew slowly. In 2010, the number of hemophilia patients was 1,678, and increased to 1,736, 1,815, and 1,841 in 2011, 2012, and 2013, respectively. The average age of the patients increased from 25.3 yr in 2010 to 27.4 yr in 2013. 97%-98% of the patients were male. Hemophilia A patients were the highest number (77%-79%), followed by Hemophilia B (17%-18%) and inhibitor patients (5%-6%). The ratio of the patients prescribed with bypassing agents increased to 5.9% in 2013 from 4.5% in 2010 (Table 1). The total CF cost in 2012 decreased slightly compared to these in 2010 and 2011. In 2010 and 2011, the cost was 162,940 USD and 158,134 USD, respectively. However, the cost in 2012 decreased to 149,427 USD. The total CF use (IU) also showed a similar tendency. Per capita CF use (IU) and per patient CF use (IU) increased during this period. In 2013, the average per patient CF cost for all hemophilia patients was 92,000 USD, while that of the patients prescribed with a bypassing agent surpassed it, reaching 516,000 USD. The cost of a bypassing agent was 5 to 10 times greater compared with the cost of other kinds of CF (FVIII or FIX), and the coefficient of variation was larger than that of the cost for FVIII or FIX prescriptions, which indicates the cost paid by patients prescribed with bypassing agents varied more compared with that paid by other hemophilia patients (Table 2).

According to the WFH database of 2012, FVIII consumption per capita for fifty countries grew slightly from 2.46 IU in 2011 to 2.76 IU in 2012. FIX for forty-seven countries also grew slightly from 0.37 IU to 0.38 IU (15). The per capita CF consumption tended to be higher for countries with a higher GNI. The CF consumption of Korea was compared to the CF consumption of twenty-eight countries whose GNI is larger than 12,196 USD (high GNI countries). In 2012, per capita FVIII usage of Korea was 3.62 IU,

**Table 1.** Demographic characteristics of Korean hemophilia patients by year

Parameters	No.(%) of patients by year				
	2010	2011	2012	2013	
Total No. of patients	1,678	1,736	1,815	1,841	
Age	Under 10	290 (17.1)	282 (16.0)	291 (15.9)	283 (15.2)
	11-19	412 (24.3)	441 (25.0)	423 (23.1)	405 (21.8)
	20-29	369 (21.8)	360 (20.4)	384 (21.0)	399 (21.5)
	30-39	292 (17.2)	306 (17.4)	319 (17.4)	323 (17.4)
	40-49	196 (11.6)	207 (11.8)	219 (12.0)	237 (12.7)
	50-59	87 (5.1)	99 (5.6)	117 (6.4)	127 (6.8)
	Over 60	48 (2.8)	66 (3.7)	77 (4.2)	86 (4.6)
Male	1,646 (98.1)	1,697 (97.8)	1,771 (97.6)	1,790 (97.2)	
Hemophilia A	1,334 (78.7)	1,374 (78.0)	1,421 (77.7)	1,426 (76.7)	
Hemophilia B	284 (16.8)	291 (16.5)	309 (16.9)	325 (17.5)	
Inhibitors patients	76 (4.5)	96 (5.5)	100 (5.5)	109 (5.9)	
Age (Mean $\pm$ SD) (yr)	25.3 $\pm$ 15.7	26.0 $\pm$ 16.3	26.8 $\pm$ 16.8	27.4 $\pm$ 17.0	

All patients had a diagnosed bleeding disorder and had received factor concentrate.

**Table 2.** Coagulation factor consumption by year

CF consumption		2010	2011	2012	2013
Total CF costs (1,000 USD)		162,940	158,134	149,427	169,816
Per-patient CF costs (1,000 USD)		97	91	82	92
FVIII	Mean	70	60	57	59
	Median	61	52	51	54
	CV	76	93	80	76
FIX	Mean	83	87	90	90
	Median	71	70	74	69
	CV	82	93	90	90
Bypassing agents	Mean	612	524	413	516
	Median	272	207	137	133
	CV	122	140	174	204
Total CF use (million IU)		2,002	2,068	1,902	2,730
Per-patient CF use (IU)					
FVIII	Mean	122,456	125,690	127,464	134,785
	Median	106,563	109,515	115,083	123,524
	CV	81	92	86	73
FIX	Mean	119,077	122,401	128,573	129,575
	Median	95,922	100,968	111,750	106,094
	CV	80	88	85	84
Bypassing agents	Mean	23,745,605	19,373,362	16,806,666	22,892,285
	Median	4,470,000	2,795,000	1,064,129	1,450,000
	CV	166	200	237	257
Per-capita CF use (IU)		3.26	3.46	3.62	3.84
FVIII		0.68	0.72	0.8	0.84
FIX		36.1	37.2	33.62	49.9
Bypassing agents					

CF, coagulation factors; FVIII, coagulation factor VIII; FIX, coagulation factor IX; CV, coefficient of variation.

which is smaller than the average usage of high GNI countries (5.36 IU). In the same year, per capita FIX usage of Korea (0.80 IU) was similar with the average of high GNI countries (0.80 IU). Per patient FVII and FIX usage in Korea were 127,464 IU and 128,573 respectively, which were higher than the average per patient FVII and FXI usage in high income countries (Fig. 1).

## DISCUSSION

The study results suggest that the CF usage and cost of Korea tended to increase slightly and that tendency could also be found for other countries (10,15,16). In Taiwan, the total annual cost of hemophilia patients increased 181% from 2001 to 2010 (11). The results from a survey for nineteen European countries revealed that the CF usage increased despite the decrease in gross domestic product and total healthcare spending (17). The increase of CF usage and cost might result from the increase per patient usage from prophylactic treatment and relatively expensive bypassing agents. The usage was expected to rise continuously as WHO and WFH recommended using CF for severe hemophilia patients as prophylactic treatment, which could improve the quality of life of patients (12,18-20). We also predicted that health care cost for hemophilia patients in Korea would increase since the number of inhibitor patients was rising and the patients spent more on drug cost and total health care cost compared with non-inhibitor patients (9).

From the CF consumption comparison of hemophilia patients in Korea and other countries of similar GNI, per capita CF usage of hemophilia patients in Korea was less than or similar to the other countries while per patient CF usage was higher. Higher per patient CF usage might result from a higher ratio of severe patients in Korea (5,6,21). In other countries, the ratio of severity level for hemophilia A patients was 40%, 24%, and 36% for severe, moderate and mild hemophilia, respectively, whereas the ratio in Korea was 69.7%, 18.6%, and 11.4%, respectively (Fig. 2). The severity ratio of hemophilia B patients in other countries was 31%, 38%, and 31%, respectively, while the ratio in Korea was 58%, 29.8%, and 11.2%, respectively (Fig. 2). This means that the ratio of severe hemophilia patients was higher in Korea. The ratios of severe hemophilia A and hemophilia B patients in Korea were 1.74 and 1.86 times higher than the WFH averages of the two types, respectively (15,22). It was obvious that per patient CF usage in Korea was large as the ratio of severe hemophilia patients in Korea was high and that the severe patients needed higher doses of CF due to clinical guidance, recommending both on-demand and prophylactic treatments.

Despite the high per patient CF usage in Korea, per capita CF usage was similar to or smaller than the global average due to the low number of hemophilia incidences. Hemophilia was present in 1 in 10,000 worldwide, while the incidences in Korea was 0.40 in 10,000, which is lower than the average for the Organization for Economic Cooperation and Development (OECD)

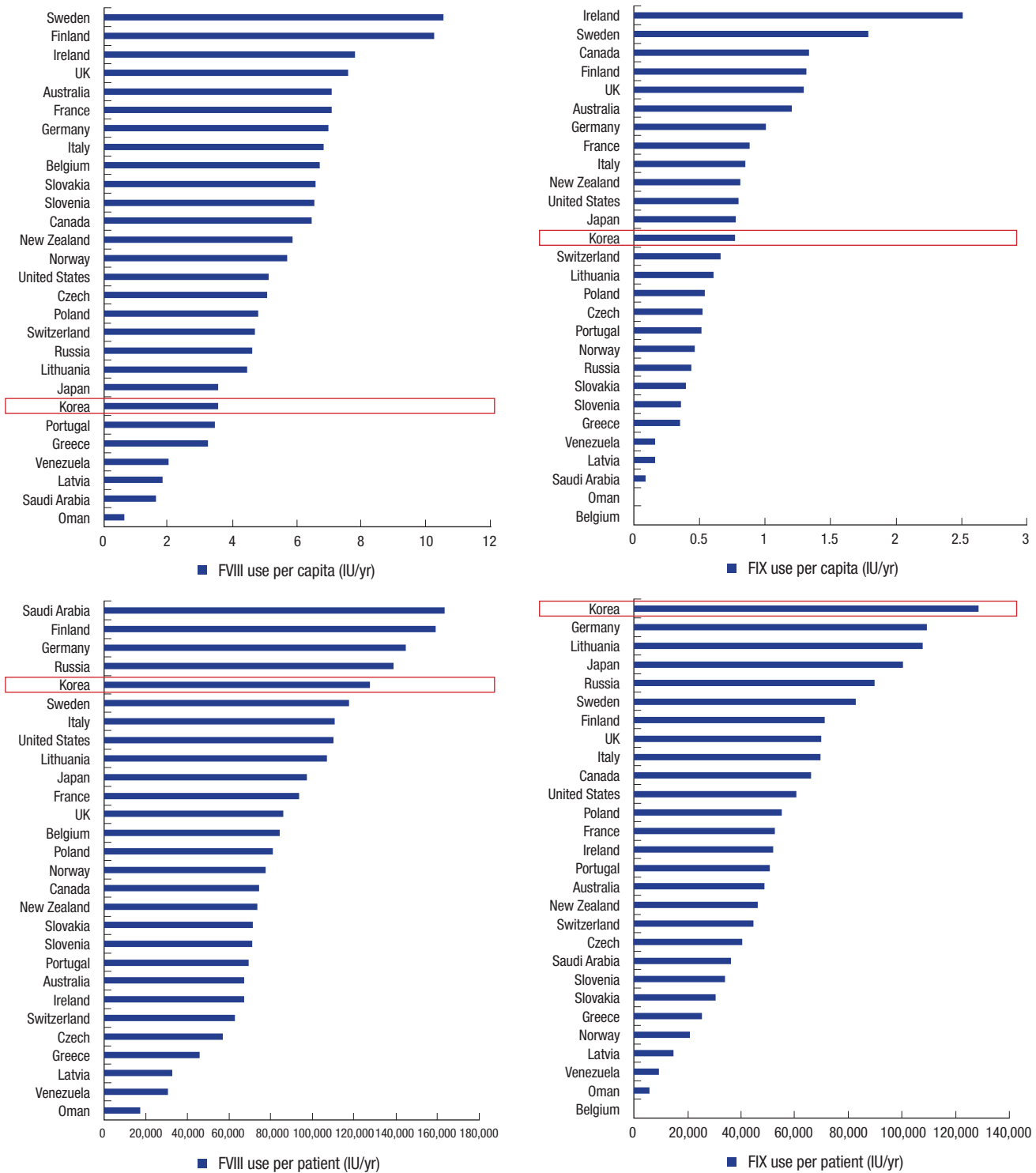
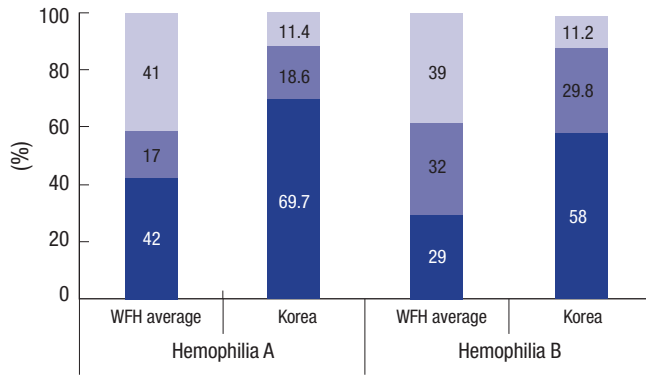


Fig. 1. Comparison of coagulation factor consumption with other high income countries. Other high income countries are whose gross national income (GNI) is larger than 12,196 USD and their data were obtained from the annual global survey (2012) of the World Federation of Hemophilia (WFH).

countries with 0.83 in 10,000 (15). This explained that per capita CF usage in Korea was similar to the global average even though per patient CF usage was very high. Nevertheless, hemophilia patients tend to avoid exposing themselves in communities which hinders the registration of patients with relatively mild

cases (5,6). Thus, there is a possibility of underestimating the prevalence rate and overestimating the proportion of patients with severe cases.

Considering that the ratio of severe incidences among hemophilia patients and the need for prophylactic treatment, it is



**Fig. 2.** Comparison of the ratio by severity level (severe, moderate, mild from bottom) for hemophilia patients with other high income countries. Other high income countries are whose gross national income (GNI) is larger than 12,196 USD and their data were obtained from the Annual Global Survey (2012) of the World Federation of Hemophilia (WFH). WFH, World Federation of Haemophilia; FVIII, Coagulation factor VIII; FIX, Coagulation factor IX.

too early to conclude that CF was abused in Korea. However, in Canada, 1.7% of CF corresponding to more than 1 million Canadian dollars was discarded due to expiration or errors in processing (12). Furthermore, the prescription compliance for CF was reported at 80%, which might result in financial waste if CF was used inefficiently or ill-managed (23). Moreover, hemophilia required continuous treatment of high cost CF (6), which demanded the efficient management of NHI resources.

The study results suggest the need for other effective programs to enhance the healthcare outcome of hemophilia treatment and to increase cost-savings to patients. In Canada, a patient registry has been developed to identify the number of patients, plans for medical study, causes of virus infections and death, and required resources (24). Canada also has operated a CF traceability program to reduce waste due to the expiration or errors in processing of CF (3). To improve the patients' self-care and treatment effects, hemophilia treatment centers (HTCs) run a disease management program or clinical tests on patients' health condition (17,25,26). Individualized education and consulting for patients by the program has improved patients' health conditions such as the reduction of bleeding or death due to complications and the reduction of cost (25,27-29).

Our study has several limitations and strengths. First, we analyzed CF usage based on prescription-based reimbursement claims data. Therefore, the CF consumption figures in this study might be overestimated because some prescriptions could not be dispensed or patients could not always take the complete regimen of the medicines dispensed. Despite the possibility of overestimating CF usage, the difference between actual usage and prescription-based reimbursement claims data should be small because Korea National Health Insurance operates numerous policies to prevent patients from misusing the expensive prescribed CF. For instance, Korea National Health Insurance has set the maximum amount allowed for prescription and num-

ber of monthly prescription, and also obliges medical institutions to complete the patient diary with the date and amount of CF consumption as well as the reason for consumption. Secondly, the subject of analysis for this study is CF prescribed patients, so the patients with mild symptoms who are not prescribed with CF are not included which may lead to underestimating the total number of hemophilia patients. In fact, the number of hemophilia patients in 2013 drawn from this study is less than the number of hemophilia patients registered at Korea Hemophilia Foundation with 1,841 and 2,196, respectively. Nonetheless, the CF usage per patient in Korea is still higher than that in other countries despite calculating CF usage per patient by using the number of hemophilia patients registered at Korea Hemophilia Foundation. Thirdly, the survey data from WFH was used in order to compare CF usage between countries, and the criteria for estimating the number of hemophilia patients may vary according to each country, which is a common error that arises in studies that use multi-national researches. However, the information provided to WFH was drawn with the best possible method by each country's national institution, so high level of accuracy can be expected (17). Furthermore, not only the twenty-seven countries that were compared in this study have similar economic level to Korea, but also most of them operate hemophilia patient registry as Korea does. Thus, even if data inaccuracy is present, it is expected to be low. Lastly, appropriateness of CF prescription could not be confirmed because we did not identify whether CF was treated as on-demand or prophylaxis, and the severity of patients and weight were not considered. Nevertheless, the study used national insurance claims data that covered 97% of the population, and thus is the first approach to investigate trends in the utilization of CFs, which consume considerable NHI resources. We also compared national insurance claims data of Korea to other countries.

In conclusion, CF usage and cost in Korea have been increasing from 2010 to 2013 and is expected to increase in the coming years. Although the present usage of CF in Korea is not excessive, it should be managed with efficient resource control due to CF's high cost. Therefore, it is necessary to collect the clinical status of hemophilia patients and monitor the health and cost outcomes by treatment.

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## DISCLOSURE

The authors have no potential conflicts of interest to disclose.

## AUTHOR CONTRIBUTION

Conception of the study: Yu SY, Lee SO. Statistical analysis: Lee SO. Manuscript preparation: Lee SO, Yu SY. Manuscript approval: all authors.

## ORCID

Soo Ok Lee <http://orcid.org/0000-0003-1671-2806>

Su-Yeon Yu <http://orcid.org/0000-0002-4192-941X>

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