Please cite this article in press as: Hatta et al., Financial risks posed by unproven cell interventions: Estimation of refunds from medical expense deductions in Japan, Stem Cell Reports (2022), https://doi.org/10.1016/j.stemcr.2022.03.015

Stem Cell Reports
Letter
ISSCR
OPEN ACCESS

Financial risks posed by unproven cell interventions: Estimation of refunds from medical expense deductions in Japan

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https://doi.org/10.1016/j.stemcr.2022.03.015

Master et al. (2021) declared that the unproven stem cell intervention (SCI) industry is a global health problem and called for the establishment of a World Health Organization (WHO) expert advisory committee on regenerative medicine to tackle this issue beyond the efforts of individual countries. We fully agree with this opinion but would like to point out that there are financial risks in addition to the health risks they listed regarding unproven SCIs. The financial risks here do not refer to the problem of patients' paying high treatment costs for SCIs with unclear scientific evidence (although, of course, this is also a serious problem). Rather, the government (i.e., the public) bears part of the cost of the treatment through a tax refund system based on medical expense deductions.

Unproven stem cell therapies have been a global issue (Berger et al., 2016), and their number is especially growing in the United States, the largest market (Turner, 2021). Our research has focused on cell-based interventions and their regulation in Japan (Kashihara et al., 2016; Ikka et al., 2015; Fujita et al., 2016). Over the past few years, we found several websites of medical institutions in Japan that included sales messages explaining that cell-based interventions are eligible for "medical expense deduction." Medical expense deduction is a tax system in which the government pays a refund to compensate for the tax burden of people who must pay large amounts of the cost of a treatment. In Japan, annual medical expenses of 100,000 to 2,000,000 yen ($877 to $17,546 and €780 to €15,600, as of January 25, 2022) are deductible from the tax payment amount, allowing patients to receive refunds from the government. Medical expenses for both "health insurance treatment" covered by the universal health insurance system and "private practice" not covered by public insurance are eligible for deductions, although some medical treatments, such as cosmetic medicine, are excluded.

The Japanese national health insurance system currently covers treatments using regenerative medical products whose safety and efficacy have been confirmed by the government (such as cell sheets for serious heart failure and severe burns) in accordance with the Act on Securing Quality, Efficacy, and Safety of Products Including Pharmaceuticals and Medical Devices (PMD act). Clinical trials demonstrating the safety and efficacy of regenerative medical products are conducted based on ICH-GCP (International Conference on Harmonization – Good Clinical Practice) guidelines. When treatment using such regenerative medical products is covered by health insurance, patients bear up to 30% of the total treatment costs, and 70% is paid by the government from insurance fees. Thus, insurance covers medical care that benefits many people.

Under private practice, cell-based interventions can be provided at medical institutions if certain procedures stipulated by the Act on the Safety of Regenerative Medicine (ASRM), such as making a provision plan that meets the implementation standards stipulated by law, which is then reviewed by a nationally certified committee, are complied with (Konomi et al., 2015). Because these cell-based interventions are not required to undergo clinical trials in general, many of them likely fall under "unproven SCI" rather than "treatment," according to the view of the International Society for Stem Cell Research (https://www.isscr.org/docs/default-source/all-isscr-guidelines/2021-guidelines/isscr-guidelines-for-stem-cell-research-and-clinical-translation-2021.pdf?sfvrsn=979d58b1_4). Therefore, cell-based interventions can be provided without providing scientific evidence at the level required by the PMD act, which is regarded by some as a problem (Cyranoski, 2019). All costs of cell-based interventions offered under private practice are paid by patients at the moment.

Although these treatments are all considered cell therapies, there is a large difference in their contents offered under the health insurance system and in private practice. Nevertheless, the medical expenses required for these treatments are equally eligible for medical expense deductions. In other words, even for unproven treatments provided by a private practice, the patient does not have to bear the full cost. In this way, the government may subsidize the cost of a private practice cell-based treatment that is based on uncertain scientific evidence. In addition, the claim on some websites of these practices that a refund can be received

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after the treatment may motivate patients to pursue the treatment.

Therefore, we estimated the total refund amount paid by the government for cell-based interventions offered under private practice in Japan, aiming to provide empirical data on the financial impact of cell-based interventions with uncertain scientific evidence on society (i.e., financial risk).

The ASRM aims at "reconstruction, repair, or formation of the structure or function of the human body" or "treatment or prevention of human diseases" and targets medical treatments using "cell processed products." The "processing" of cells refers to "performing drug treatment, modification of biological properties, and combination with non-cell components or genetic engineering modification for artificial proliferation and differentiation of cells and tissues, establishment of cell lines, and cell activation," excluding blood transfusions, hematopoietic stem cell transplantations, and assisted reproductive technologies. Therefore, in addition to stem cell-based interventions, the results below include cancer immunotherapy and platelet-rich plasma therapy. In this study, the treatments provided according to the ASRM are referred to as "cell-based interventions."

The refund amount paid to patients by the government indicates the amount of medical expense deduction (for annual medical expenses of 100,000 yen or more, a maximum of 2,000,000 yen is covered from the total medical expenses after subtracting 100,000 yen) multiplied by the income tax rate. However, because the amount of the medical expense deduction and income tax rate vary greatly from person to person, it is practically difficult to determine these two values individually. Therefore, we (1) estimated the mean amount of the medical expense deduction per case of approved cell-based intervention on the basis of documents published for patients by the Ministry of Health, Labour, and Welfare (MHLW) in Japan; (2) calculated the average income tax rate by prefecture on the basis of the information published by the Ministry of Internal Affairs and Communications; and (3) determined the average refund amount per case of cell-based intervention by prefecture on the basis of (1) and (2). By multiplying this average by the annual number of patients (or the number of injections; both published by the MHLW) by prefecture, we calculated the annual amount of refund for each prefecture and totaled the amounts to determine the total annual amount of refund for the whole country (see the supplemental information for details).

According to the information published by the MHLW, 37,911 people received a total of 70,810 cell-based interventions in 2017, and 67,407 people received a total of 113,550 cell-based interventions in 2018. Using the method described above, the total annual amount of medical expenses for cell-based interventions for the number of patients was estimated as 1.0 billion to 79.5 billion yen (median 7.1 billion yen) in 2017 and 1.8 billion to 141.4 billion yen (median 12.7 billion yen) in 2018. On the basis of the number of injections, the estimated amount was 1.9 billion to 148.5 billion yen (median 13.3 billion yen) in 2017 and 3.0 billion to 238.2 billion yen (median 21.3 billion yen) in 2018. The total annual amount of refund for the number of patients was estimated to be 105.4 million to 8.2 billion yen (median 881.6 million yen) in 2017 and 191.3 million to 14.9 billion yen (median 1.6 billion yen) in 2018. On the basis of the number of injections, the estimated amount was 201.9 million to 15.8 billion yen (median 1.7 billion yen) in 2017 and 325.7 million to 238.2 billion yen (median 2.7 billion yen) in 2018 (see Table S5 in the supplemental information for the respective amounts converted to US dollars and euros).

We recognize that this survey estimated only the costs and number of treatments on the basis of the materials published by the government. In addition, not all patients apply for the medical expense deduction. These facts must be considered when interpreting the results of this survey.

Nevertheless, our findings estimate that the total refund amount for private practice cell-based interventions, including unproven SCIs, is in the hundreds of millions of yen per year. Thus, a substantial amount of public funds—not only as treatment costs paid by the patients but also as taxes—is spent even on treatments with uncertain scientific evidence. In other words, financial risks posed by unproven cell-based interventions, particularly SCIs, are not only private issues for patients but also public issues. Although revisions to the ASRM are currently being discussed (Takashima et al., 2021), the estimates in this study argue that serious consideration be given to whether the ASRM should continue to allow the provision of unproven cell-based interventions. Moreover, it is likely similar financial risk exists in other countries as well. In fact, private practices in other countries highlight similar deductions (Turner, 2018). Investigations and reports from other countries are needed to determine whether those countries too are incurring similar financial risks for unproven cell-based interventions, especially SCIs.

WEB RESOURCES

ISSCR Guidelines for Stem Cell Research and Clinical Translation, https://www.isscr.org/docs/default-source/all-isscr-guidelines/2021-guidelines/isscr-guidelines-for-stem-cell-research-and-clinical-translation-2021.pdf?sfvrsn=979d58b1_4

SUPPLEMENTAL INFORMATION

Supplemental information can be found online at https://doi.org/10.1016/j.stemcr.2022.03.015.

AUTHOR CONTRIBUTIONS

T.I. conceived the study. T.H. designed the equations to implement the ideas and collected and analyzed the data with K.I. M.F. supervised the process from the equation design to the analysis. All authors contributed to the data interpretation, participated in discussions on important intellectual content, wrote the manuscript, and approved the final manuscript.

CONFLICTS OF INTEREST

The authors declare no competing interests.

ACKNOWLEDGEMENTS

We are grateful to Dr. Yuichi Imanaka (Kyoto University, Japan) and Dr. Peter Karagiannis (Kyoto University, Japan) for providing expert advice and to Knowledge Data Service (Kyoto, Japan) for dataset preparation. This study was funded by the JSPS KAKENHI Grant-in-Aid for Scientific Research (grants 18K13110, 21K10326, and 17K13665) and the Uehiro Foundation on Ethics and Education.

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Stem Cell Reports, Volume *17*

Supplemental Information

Financial risks posed by unproven cell interventions: Estimation of refunds from medical expense deductions in Japan

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Supplemental Information

The "Act on the Safety of Regenerative Medicine (ASRM)" aims at "reconstruction, repair, or formation of the structure or function of the human body" or "treatment or prevention of human diseases" and targets medical treatments using "cell processed products." "Processing" of cells refers to "performing drug treatment, modification of biological properties, and combination with non-cell components or genetic engineering modification for artificial proliferation and differentiation of cells and tissues, establishment of cell lines, and cell activation," excluding blood transfusion, hematopoietic stem cell transplantation, and assisted reproductive technology. Therefore, in addition to stem cell-based interventions, the results below include cancer immunotherapy and platelet-rich plasma therapy. In this study, the treatments approved by ASRM are referred as "cell-based interventions."

1) Average amount of medical expense deduction per case of cell-based intervention
Since the revision of the ASRM enforcement regulations on November 30, 2017, the website of the Ministry of Health, Labour, and Welfare (MHLW) has published the names of implementation facilities, names of cell-based interventions, and explanatory consent documents used at the facilities[1]. Of 3,536 cases of cell-based interventions approved as treatment, we extracted the target diseases (Table S1), cells used (Table S2), and prices from the explanatory documents of 3,467 cases, excluding 69 cases in which the treatment details could not be obtained, by accessing the website of the MHLW between December 2017 and February 2018. Cell-based interventions were categorized into 24 types based on the combination of the extracted target disease and cells used, and the number of cases of cell-based intervention for each type was identified. As some documents did not list the prices of cell-based interventions, we extracted the lower limit, median, and upper limit of the prices (Table S3).

Then, assuming that these prices were the annual medical expenses for cell therapies (Table S3, Cost), we calculated the amount of medical expense deduction (Table S3, Deduction) as follows: (1) 100,000 yen was subtracted from the minimum, maximum, and median treatment costs for each type, (2) the upper limit was 2 million yen even if the amount exceeded this limit, and (3) the amount corresponding to cosmetic medicine was considered as 0 yen. According to the International Monetary Found, the average annual rates for 2017 were

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[1] Website of the MHLW
(https://www.mhlw.go.jp/stf/seisakunitsuite/bunya/0000186471.html)

JPY112. 2/USD and EUR0.89/USD. The average annual rates for 2018 were JPY110. 4/USD and EUR0.85/USD.[2]

Furthermore, the average amount of medical expense deduction per treatment case was calculated by multiplying the amount of medical expense deduction estimated for each type (Table S3, Deduction) by the number of cases of cell-based intervention for each type and dividing the total amount by the total number of treatment cases. This is synonymous with the expected value of the amount of medical expense deduction for patients who received cell-based interventions, including the minimum amount shown in Equation 1, for example.

$$\bar{x}_{min} = \sum_{k=1}^{24} \frac{n_k}{3460} \times x_{min,\ k}$$

・・・Equation 1

$\bar{x}_{min}$: Expected value of the minimum amount of medical expense deduction, n_k: Number of cases for treatment type k

$x_{min,\ k}$: Minimum amount of medical expense deduction for treatment type k

k: [1,…, 24] = [Cancer_NKT cells, …, Undetectable_Fibroblasts]

2）Mean income tax rate by prefecture

Referring to the "Survey of municipal taxation status" (Ministry of Internal Affairs and Communications, 2018; 2019)[3] [4], mean taxable income was calculated by dividing the total taxable income of the capital of each of the 47 prefectures at the time of the survey by the number of taxable persons, and the corresponding income tax rate (divided into 7 levels of 5–45%) was identified by prefecture (Table S4).

3）Total annual amount of refund for the whole country

The average amount of refund per case of cell-based intervention was calculated by prefecture based on the average amount of medical expense deduction per case and income tax rate identified by prefecture as determined above. By multiplying this with the annual number of patients (or the number of injections; both published by the MHLW) by prefecture, the

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[2] Website of the IMF Data(https://data.imf.org)

[3] Ministry of Internal Affairs and Communications (2018) The 2017 survey of municipal taxation status (Table 11)

[4] Ministry of Internal Affairs and Communications (2019) The 2018 survey of municipal taxation status (Table 11)

amount of annual refund was calculated for each prefecture. After revising the ASRM enforcement regulations, the annual number of patients and number of injections by prefecture are published by the MHLW based on the annual report from each implementing facility (MHLW, 2018; 2019)[5] [6]. By totaling the annual amount of refund for each prefecture estimated by this method, the total annual amount of refund for the whole country was determined (Table S5). For example, the minimum total amount of refund for 2017 was calculated as shown in Equation 2. These mathematical calculations were performed by Python 3.7.11 (Python Software Foundation, Beaverton, OR).

$$y_{min,2017,patient} = \sum_{i=1}^{47} p_{2017,i} \times \bar{t}_{2017,i} \sum_{k=1}^{24} \frac{n_k}{3460} \times x_{min,k}$$
$$= \sum_{i=1}^{47} p_{2017,i} \times \bar{t}_{2017,i} \times \bar{x}_{min}$$

・・・Equation 2

$p_{a,i}$: Number of patients in prefecture i in 2017

$\bar{t}_{a,i}$: Income tax rate per taxpayer in prefecture i in 2017

$x_{min,\ k}$: Minimum amount of medical expense deduction for treatment type k

n_k: Number of cases for treatment type k

i: [1,⋯,47] = [Hokkaido, ⋯, Okinawa Prefecture]

k: [1,⋯, 24] = [Cancer_NKT cells, ⋯, Undetectable_ Fibroblasts]

[5] MHLW (2018) Outline of the compilation of regular reports on the provision status of regenerative medicine

[6] MHLW (2019) Outline of the compilation of regular reports on the provision status of regenerative medicine

Table S1. Target diseases of cell-based interventions offered as treatment under private practice

	n	%
Dental Treatment	1,513	43.6%
Cancer Treatment	1,175	33.9%
Cosmetic Medicine	543	15.7%
Others	99	2.9%
Undetectable	137	4.0%
not eligible	69	

Table S2. Cells used in cell-based interventions offered as treatment under private practice

Cell	n
Platelets	2072
Lymphocytes	545
NK cells	422
Dendritic cells	267
Adipose-derived regenerative cells, adipose-derived regenerative stem cells	47
Fibroblasts	37
Adipose cells, adipose stem cells	33
Mesenchymal stem cells	23
NKT cells	5
Bone marrow cells	5
Epidermal cells	4
Mononuclear cells/monocytes	2
Immune cells	2
Stromal vascular fraction cells	1
Periosteal cells	1
Cartilage cells	1

Table S3. Costs of cell-based interventions offered as treatment under private practice and the amount of medical expense deduction

Combinations of target diseases and cells	n	Cost (JPY)			Deduction (JPY)		
		Min	Max	Median	Min	Max	Median
Cancer_NKT cells	5	2,160,000	2,500,000	2,336,480	2,000,000	2,000,000	2,000,000
Cancer_NK cells	415	5,400	4,518,180	313,200	0	2,000,000	313,200
Cancer_Lymphocytes	524	8,000	4,879,634	270,000	0	2,000,000	270,000
Cancer_Dendritic cells	231	8,000	3,240,000	310,240	0	2,000,000	310,240
Dental_Platelets	1510	2,000	1,000,000	11,000	0	1,000,000	11,000
Dental_Adipose cells, adipose stem cells	1	108,000	108,000	108,000	8,000	108,000	108,000
Cosmetic_Mesenchymal stem cells	4	648,000	648,000	648,000	0	0	0
Cosmetic_Platelets	472	20,000	324,000	116,640	0	0	0
Cosmetic_Adipose cells, adipose stem cells	7	90,000	756,000	423,000	0	0	0
Cosmetic_Adipose-derived regenerative cells, adipose-derived regenerative stem cells	45	25,000	1,420,000	848,000	0	0	0
Cosmetic_Fibroblasts	10	507,600	1,080,000	507,600	0	0	0
Cosmetic_Epidermal cells	4	1,214,230	1,214,230	1,214,230	0	0	0
Others_Mesenchymal stem cells	17	432,000	3,942,000	1,620,000	332,000	2,000,000	1,520,000
Others_Platelets	51	10,000	108,000	32,400	0	8,000	0
Others_Bone marrow cells	5	259,905	4,330,800	2,700,000	159,905	2,000,000	2,000,000
Others_Adipose cells, adipose stem cells	21	200,000	3,240,000	864,000	100,000	2,000,000	764,000

Others_Adipose-derived regenerative cells, adipose-derived regenerative stem cells	2	800,000	800,000	800,000	700,000	700,000	700,000
Others_Mononuclear cells/monocytes	2	100,000	100,000	100,000	0	0	0
Undetectable_NK cells	7	270,000	270,000	270,000	170,000	170,000	170,000
Undetectable_Lymphocytes	21	81,648	226,800	226,800	0	126,800	126,800
Undetectable_Platelets	39	2,820	250,000	50,000	0	150,000	0
Undetectable_Adipose cells, adipose stem cells	4	648,000	1,620,000	864,000	548,000	1,520,000	764,000
Undetectable_Dendritic cells	36	380,000	2,659,392	2,103,300	280,000	2,000,000	2,000,000
Undetectable_Fibroblasts	27	410,400	1,166,400	710,000	310,400	1,066,400	610,000

The average annual rates for 2017 were JPY112. 2/USD and EUR0.89/USD.

The average annual rates for 2018 were JPY110.4/USD and EUR0.85/USD.

Seven cases whose prices had not been listed were not included in the table, even though they were analysis subjects.

Table S4. Mean income tax rate by prefecture

Prefectures	Mean income tax rate in 2017	Mean income tax rate in 2018
Hokkaido	0.1	0.1
Aomori	0.1	0.1
Iwate	0.1	0.1
Miyagi	0.2	0.2
Akita	0.1	0.1
Yamagata	0.1	0.1
Fukushima	0.1	0.1
Ibaraki	0.2	0.2
Tochigi	0.2	0.2
Gunma	0.1	0.2
Saitama	0.2	0.2
Chiba	0.2	0.2
Tokyo	0.2	0.2
Kanagawa	0.2	0.2
Niigata	0.1	0.1
Toyama	0.1	0.1
Ishikawa	0.1	0.2
Fukui	0.1	0.1
Yamanashi	0.1	0.2
Nagano	0.1	0.1
Gifu	0.2	0.2
Shizuoka	0.1	0.2
Aichi	0.2	0.2
Mie	0.1	0.1
Shiga	0.2	0.2
Kyoto	0.2	0.2
Osaka	0.2	0.2
Hyogo	0.2	0.2
Nara	0.2	0.2
Wakayama	0.1	0.1

Tottori	0.1	0.1
Shimane	0.1	0.1
Okayama	0.1	0.1
Hiroshima	0.2	0.2
Yamaguchi	0.1	0.1
Tokushima	0.1	0.1
Kagawa	0.1	0.1
Ehime	0.1	0.1
Kochi	0.1	0.1
Fukuoka	0.2	0.2
Saga	0.1	0.1
Nagasaki	0.1	0.1
Kumamoto	0.1	0.1
Oita	0.1	0.1
Miyazaki	0.1	0.1
Kagoshima	0.1	0.1
Okinawa	0.1	0.1

Data sauces: Ministry of Internal Affairs and Communications (2018) The 2017 survey of municipal taxation status (Table 11) URL https://www.soumu.go.jp/main_sosiki/jichi_zeisei/czaisei/czaisei_seido/ichiran09_17.html; and Ministry of Internal Affairs and Communications (2019) The 2018 survey of municipal taxation status (Table 11) URL https://www.soumu.go.jp/main_sosiki/jichi_zeisei/czaisei/czaisei_seido/ichiran09_19.html.

Table S5. Estimated annual treatment costs and refund for cell therapies offered as treatment under private practice

	Year	Patients			Injections		
		Min	Max	Median	Min	Max	Median
Cost (JPY)	2017	1,009,679,861 (USD 8,998,929) (EUR 8,009,047)	79,520,180,227 (USD 708,736,009) (EUR 630,775,048)	7,119,903,186 (USD 63,457,248) (EUR 56,476,950)	1,885,875,629 (USD 16,808,161) (EUR 14,959,263)	148,527,444,854 (USD 1,323,774,018) (EUR 1,178,158,876)	13,298,524,032 (USD 118,525,170) (EUR 105,487,401)
	2018	1,795,243,871 (USD 16,261,267) (EUR 13,822,077)	141,389,485,599 (USD 1,280,701,862) (EUR 1,088,596,583)	12,659,421,119 (USD 114,668,670) (EUR 97,468,369)	3,024,165,762 (USD 27,392,806) (EUR 23,283,885)	238,176,689,213 (USD 2,157,397,547) (EUR 1,833,787,915)	21,325,341,108 (USD 193,164,322) (EUR 164,189,673)
Refund (JPY)	2017	105,395,196 (USD 939,351) (EUR 836,022)	8,226,964,876 (USD 73,324,108) (EUR 65,258,456)	881,572,126 (USD 7,857,149) (EUR 6,992,863)	201,877,299 (USD 1,799,263) (EUR 1,601,344)	15,758,189,307 (USD 140,447,320) (EUR 124,998,115)	1,688,591,195 (USD 15,049,832) (EUR 13,394,351)
	2018	191,294,519 (USD 1,732,740) (EUR 1,472,829)	14,932,116,014 (USD 135,254,674) (EUR 114,966,473)	1,600,072,136 (USD 14,493,407) (EUR 12,319,396)	325,742,269 (USD 2,950,564) (EUR 2,507,979)	238,176,689,213 (USD 2,157,397,547) (EUR 1,833,787,915)	2,724,652,694 (USD 24,679,825) (EUR 20,977,851)

The average annual rates for 2017 were JPY112. 2/USD and EUR0.89/USD.

The average annual rates for 2018 were JPY110. 4/USD and EUR0.85/USD.

The total amount paid for cell interventions by the Japanese patient population is “Cost” minus “Refund.” For example, the minimum amount paid by patients for cell interventions in 2017 was 1,009,679,861 - 105,395,196 = JPY904,284,665.