Integrated Collection of Stem Cell Bank data, a

data portal for standardized stem cell information

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SUMMARY

The last decade has witnessed an extremely rapid increase in the number of newly established stem cell lines worldwide. However, due to the lack of a standardized format, data exchange among stem cell line information resources has been challenging, and no system can search all stem cell lines across resources worldwide. To solve this problem, we have developed the Integrated Collection of Stem Cell Bank data (ICSCB) (http://icscb.stemcellinformatics.org/), a new and largest database search portal for stem cell line data from various resources, based on the standardized data items and terms of the MIACARM framework. Currently, ICSCB can retrieve 15,796 cell lines from four major data resources in Europe, Japan, and the U.S. ICSCB is automatically updated to provide the latest cell line information, and its integrative search engine helps users collect cell line information from donors with rare diseases worldwide, which has been a formidable task, thereby distinguishing itself from other database search portals.

INTRODUCTION

Since the first report of human induced pluripotent stem cells (iPSCs) (Takahashi et al., 2007), there has been a rapid rise in the number of iPSC lines and related information worldwide **(Table 1)**. This remarkable growth has not only accelerated studies of regenerative medicine but also provided opportunities to understand such pragmatic issues as the quality of pluripotent stem cells (Nishizawa et al., 2016) and the disease mechanisms (Sasaki et al., 2016). Stem cell banks and registries are expected to provide necessary data of individual stem cell lines. However, the exchange of data among different institutions is not a trivial matter, and scientific reproducibility based on available information is problematic for both basic studies and clinical applications (Yaffe et al., 2016; Isasi and Knoppers, 2011; Thirumala et al., 2009). Moreover, as technologies for the characterization of cell lines continue to progress, the addition of new quality standards as necessary data items is complicating and diversifying data formats among different stem cell banks and registries (Hug, 2009; Knoppers and Isasi, 2010). As an attempt to solve these problems, we previously reported MIACARM (Minimum Information About a Cellular Assay for Regenerative Medicine) guidelines in

2016 (Sakurai et al., 2016), which proposed the utilization of standardized data items and

formats for all stem cell lines in regenerative medicine. Presently, MIACARM contains

258 items, covering such areas as stem cell production and materials (e.g., donor

information, source cell information, and cell culture medium and substrate information),

cell banking processes, cell characterization, sterility testing, and even ethical concerns.

Later, a standardized nomenclature for pluripotent stem cells was introduced in 2018 with

unification of cell line codification and minimization of information loss and confusion

regarding cell lines as goals (Kurtz et al., 2018). Nevertheless, with the growing number

of registered cell lines, existing data deposition formats have made it increasingly harder

for not only data depositors but also users to seek and obtain cell lines collected under

different projects, disease status, and privacy issues (Godard et al., 2003; Winickoff et al.,

2009).

86   In this paper, as our next step towards the unification and utilization of stem

cell line data in the world, we report our new database portal, Integrated Collection of

Stem Cell Bank data (ICSCB), which was designed using MIACARM guideline items

and formats. The main objectives of ICSCB are i) to establish an integrated stem cell

database portal that can cover the majority of stem cell resources in the world, and ii) to

offer users minimum but efficient access to information on stem cell lines based on

MIACARM guidelines. Currently, ICSCB provides data of more than 15,000 stem cell

lines registered in four major stem cell line databases: hPSCreg (Seltmann et al., 2015),

SKIP (Kim et al., 2017), RIKEN BRC (Kobayashi et al., 2016), and eagle-i (Vasilevsky et

al., 2012). ICSCB has a user-friendly search engine for stem cell lines and can be

accessed directly at http://icscb.stemcellinformatics.org/, or as a slim version by

removing cell line redundancy as much as possible through the SHOGoiN (Human

Omics Database for the Generation of iPS and Normal Cells) homepage at

http://shogoin.stemcellinformatics.org/.

RESULTS AND DISCUSSION

Web interface

ICSCB was designed for researchers searching for available cell lines to conduct various

studies, such as regenerative medicine and disease analysis. Covering as many diverse

cell lines as possible was the first priority when deciding which resources to include in

ICSCB. Sharing cell line information between different stem cell banks and registries is

problematic due to different cell naming methods, different policies on cell assessment in

different registries, unclear data sources, and so on. ICSCB is a collection of cell lines

from four major and reliable cell line data resources based in Europe, Japan, and the

United States. ICSCB updating is regularly performed for new SKIP and eagle-i stem cell

line data as well as automatically performed for hPSCreg and RIKEN BRC data in a

synchronized manner. Users can retrieve all related stem cell line information by using a

free text search. Detailed information for a specific cell line can be accessed by clicking

on the stem cell ID, which is linked to the information page in the original resources

(**Figure 1**). The results can be further filtered according to users' requests. There may be

several records for the same cell line if the cell line is included in multiple data resources.

To provide users as much information as possible, the results page is designed to show

cell lines with matching cell names as well as close descriptions.

Data coverage

ICSCB covers more data than any other stem cell line repository available. The

integration of all major data resources allows us to check the current state of stem cell

research in the world **(Figure 2)**. Although we recognize redundancies in the data,

according to our statistics, the number of iPSC lines constitutes more than 80% of all cell

lines and the ratio of healthy to diseased donors is approximately 3 to 2 **(Figure 2A,B)**.

The total number of countries from which cell lines can be retrieved is 36 (as of March

26, 2020), of which the top 9 countries identified in SKIP and hPSCreg are (in descending

order) the United Kingdom, United States, Japan, Germany, China, Spain, Sweden,

Denmark, and Italy **(Figure 2C)**. In addition, as the recent number of iPSC lines

generated from patient donors is growing, ICSCB supports disease-oriented search to

help users find all disease-related stem cell lines by using disease names. The distribution

of disease and disorder types is shown in **Figure 2D**.

Easy search interface on SHOGoiN homepage

ICSCB also has a quick and easy search module on the SHOGoiN homepage

(https://stemcellinformatics.org/). SHOGoiN is a repository for accumulating and

integrating diverse human cell information to support a wide range of research using

cell-related data. The database consists of several modules that store cell lineage maps,

transcriptomes, methylomes, cell conversions, cell type markers, and cell images with

morphology data curated from public as well as contracted resources based on

sophisticated cell taxonomy. Collaboration between ICSCB and SHOGoiN makes it

possible for users to directly use free text searches for stem cell line data on the

SHOGoiN homepage. The ICSCB easy search module in SHOGoiN supports a

simplified ICSCB search with keywords, and the advanced search is designed to redirect

users to the ICSCB homepage with full functions. Results from the SHOGoiN

homepage share the same structure with the ICSCB homepage.

Concluding remarks and future plan

So far, the registration and submission of newly established cell lines have been

complicated by the lack of standardized data formats. Most data registries are currently

limited by respective domestic policies and have adopted their information structures and

validation processes independently (Andrews et al., 2015; Zarzeczny et al., 2009). The

lack of standardized data formats has caused problems for researchers who must usually

search several websites to find the stem cell lines they are looking for (Wells et al., 2013).

In the present work, we developed ICSCB, an integrated data distribution system that

provides stem cell line information from major stem cell banks and registries all over the

world. ICSCB adopts a standardized information format based on the "Source Cell"

module of MIACARM to integrate different data resources while keeping important

information.

In the future, in order to respond to the rapid growth in the number of stem cell

lines, we will include more data resources in ICSCB, including the Taiwan Human

Disease iPSC Service Consortium and other recently developed stem cell banks, to make

ICSCB more resource-abundant and usable. We also plan to add a detailed quality check

to help users find stem cell lines of high quality. As the largest stem cell line information

resource, we will support stem cell communities by improving the quality and increasing

the scale of our database.

EXPERIMENTAL PROCEDURES

Data resources

ICSCB resources were selected from existing major stem cell registries that collect cell

line information in Europe, Japan, and the U.S., and stem cell banks that provide cell lines

with information of the attributes. We checked the number of registered cell lines and the

criteria for registration in these registries and banks to decide to what extent their cell line

data can fulfill MIACARM guidelines for inclusion in ICSCB. Considering the size,

accessibility, and diversity of the different databases, three stem cell registries and one

stem cell bank were included: (1) SKIP (5,615 cell lines), (2) hPSCreg (3,099 cell lines),

(3) RIKEN BRC (3,534 cell lines), and (4) eagle-i (3,548 cell lines) (as of March 26,

2020). These data resources were selected because they had the highest number of

registered cell lines and large diversity, which would provide a good regional balance of

cell sources to reduce redundancies in cell line entries. RIKEN BRC basically collected

cell lines from Japanese institutions, SKIP contained data mostly from other Japanese and

Asian institutions, hPSCreg collected data mainly from European institutions, and eagle-i

collected data mostly from the United States. Details of the data sources are listed in

Figure 3.

Data integration

Since our previous research on the listed stem cell banks (Sakurai et al., 2016), the

number of registered cell lines had skyrocketed from 1,483 to approximately 8,000 in the

past three years. As a result, stem cell registries are facing the demand to collect

information on the rapidly increasing number of new cell lines and register the cell lines

into their databases as quickly as possible. However, because the stem cell banks and

registries are using their own formats for data entry, the integration of the data into a

centralized collection system is an extraordinary challenge. To solve this problem, we

used a decentralized or distributed database system (Fujibuchi et al., 1998) by adopting

items of different database formats into 12 attributes, or terms, from three MIACARM

modules: stem cell general identification, donor identification, and source cell

identification (**Table 2**). To practically integrate the data from the four data resources

(SKIP, hPSCreg, RIKEN BRC, and eagle-i), we adopted a mechanism of cross-reference

tables that allow users to conduct a search using MIACARM terms that are translated into

the corresponding terms in the individual data resources to implement the search. For

example, the term "Stem cell ID" in MIACARM was translated into the terms "stem cell

id" (hPSCreg), "stem cell id" (SKIP), "CellID" (RIKEN BRC), and "cell line label"

(eagle-i) for the search implementation. Thus, ICSCB submits search requests to each

data resource with its own (translated) terms and integrates all retrieved results by

common MIACARM terms, thereby achieving a standardized data format at the level of

display (**Figure 4**).

ICSCB workflow and search engine updating

In order to provide fast and easy access to the latest and accurate cell line information, we

built an automatic updating system that adds newly released cell lines to ICSCB as soon

as they become available in any of the four data resources. Data from eagle-i and SKIP

are directly collected and stored in the MySQL database with the terms required for the

MIACARM modules. Data from hPSCreg and RIKEN BRC are collected on the fly per

request using a web application programming interface (API) provided by the respective

sites. RIKEN BRC also uses SPARQL language for data retrieval requests (Kim et al.,

2017; Kobayashi et al., 2016).

To simplify the search process, ICSCB provides an easy-to-use and

mobile-friendly web application. The goal of the application is to help users find the

desired stem cell lines as quickly as possible. The interface of the search engine is

designed with the 12 MIACARM terms (**Table 2**) except the term "Stem cell ID". Users

receive result pages with all the matching results listed in a table that includes all the basic

attributes under the structure of MIACARM. To ensure a more specific search with a

wide variety of attributes, ICSCB is designed to accommodate searches not only by

standardized terms from MIACARM but also by terms specific to each of the four data

resources, such as "age" or "country" (**Figure 5A**). When user queries are submitted,

ICSCB simultaneously retrieves MIACARM standardized data and resource-specific

data so as not to miss any relevant entries. If a keyword entered by a user in a general

keyword search does not exist in MIACARM terms but is included in data specific to any

of the four data resources, the user will get detailed descriptions of the matching data in

the results page. For example, even if the standardized MIACARM terms do not contain

"transgene", it is still possible to enter a gene name into the keyword field (e.g., Sox2)

such that the results page will display relevant entries by showing the indicated keyword

in the extra field below **(Figure 5B)**. Furthermore, the user can filter the results by data

resource and detailed keywords from "Searching options" box inside the results page to

narrow down the results list. In addition, all the results can be easily downloaded as a

table directly from the results page.

In addition, ICSCB provides a quality control panel based on MIACARM,

supporting customized searches according to quality control results. At present, assays

for teratoma formation, differentiation ability in vitro, morphology data, marker gene

expression/surface antigen expression data, karyotyping assay results, copy number

variation, residual exogene detection results, genome profiling, transcriptome profiling,

and epigenome profiling data are accessible from ICSCB.

SUPPLEMENTAL INFORMATION

Supplemental Information includes Supplemental Experimental Procedures, three

figures, and five tables, and can be found with this article online at:

AUTHOR CONTRIBUTIONS

YC and YP drafted the manuscript. SM, TM, HO, JD, SS, AK, HM, YN, MS, JS, and

WF provided and facilitated the stem cell data. WF conceptualized the research. AK,

GS, and WF led the project.

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COMPETING INTERESTS

H.O. is a founding scientist of SanBio Co., Ltd. and K Pharma Inc.

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FIGURE LEGENDS

Fig. 1: Web interface of ICSCB.

(A) The ICSCB search page. Any keyword related to cell lines (including cell line name,

disease name, gender, and so on) can be used to perform an instant search. (B) The

ICSCB results page. Matched or partially matched cell lines are listed according to

MIACARM terms. To check the details of the cell lines, the user can click on the stem cell

ID, which is linked to the original source of cell line information.

Fig 2. **Details of cell lines collected by ICSCB**.

Cell line information is categorized as (A) stem cell type, (B) health/disease status of

donor, (C) country that established the cell lines, and (D) disease category.

Fig. 3: Overview of ICSCB.

ICSCB includes data from three stem cell registries and one cell bank in order to

maximize data coverage worldwide.

Fig. 4: Workflow of ICSCB data integration.

The SKIP and eagle-i databases were fully replicated from websites and imported to

MySQL (even when updating ICSCB), whereas hPSCreg and RIKEN BRC used a web

API and SPARQL for data collection. Cross-reference tables (Table 3) were used when

ICSCB integrated and standardized cell line data.

Fig. 5: Keyword search is automatically extended to all terms provided by the four

data resources even if a keyword is not included in standardized MIACARM

terms.

(A) Terms specific to each of the four data resources. (B) Even if the standardized

MIACARM terms do not contain, for example, "transgene", it is still possible to enter a

gene name into the keyword field (e.g., Sox2), which will lead users to results from the

four data resources with relevant information. The results of the match will be shown in

another row below the standardized fields.

Fig1 Interface

A

Integrated Collection of Stem Cell Bank data by MIACARM

○ What's New

| 2019.12.01 | Cell lines from SKIP database has been updated. |
| 2019.10.01 | Japanese version of the ICSCB has been released. |

B

Integrated Collection of Stem Cell Bank data by MIACARM

Items: 1 ~ 100 / 15656

Data source							Source cell				
				Stem cell production							
	Stem cell general identification						Donor identification			Source cell identification	
	Stem cell ID	Stem cell name	Stem cell type	Cell grade	Produced by	Provider/ distributor	Reference publication	Gender of donor	Ethnicity of donor	Health status of donor	Source cell type	Organ/tissue of origin of source cell
SKIP	SKIP000001	201B7	iPS Cell	Research Grade	Yamanaka Shinya	Center for iPS Cell Research and Application, Kyoto	18035408 23300777 27073925 27161380	Female	Caucasian			Skin
SKIP	SKIP000002	253G1	iPS Cell		Yamanaka Shinya	Center for iPS Cell Research and Application, Kyoto		Female	Caucasian			Skin
SKIP	SKIP000003	iPS-TIG107 3f1	iPS Cell		Yamanaka Shinya	Center for iPS Cell Research and Application, Kyoto	18035408	Female	Asian			Skin
SKIP	SKIP000004	iPS-TIG107 4f1	iPS Cell		Yamanaka Shinya	Center for iPS Cell Research and Application, Kyoto	18035408	Female	Asian			Skin

As of March 26, 2020

Fig2 Pie chart

A Stem cell type

ES Cells 5.56%
Others 7.81%
IPS Cells 81.4%

B Health status of donor

Diseased 39.1%
Healthy 60.9%

C Country*

United Kingdom	29.5 %
United States	20.1%
Japan	17.2 %
Germany	14.2 %
China	4.8%
Spain	2.7 %
Sweden	2.2 %
Denmark	2.1 %
Italy	1.7 %
Others	14.2 %

*only data from SKIP databases and hPSCreg are included

Cell line count

D Disease/Disorder

Nervous System	45.1%
Genetic	13 %
Endocrine System	8%
Cardiovascular	7.9 %
Mental	6.7 %
Musculoskeletal	3.8 %
Eye	3.8 %
Urogenital	1.9 %
Hemic and Lymphatic	1.9 %
Male Urogenital	1.7 %
Nutritional and Metabolic	1.5 %
Neoplasm	1.1%
Immune System	1 %
Skin and Connective Tissue	0.9 %
Chemically Induced	0.3 %
Digestive System	0.2 %
Others	1.2 %

As of March 26, 2020

Disease count

Database	Registry/Bank(Country)	Countries from which data were acquired
SKIP	**Registry(Japan)** skip.stemcellinformatics.org/en/	**Australia; Canada; China; Czech Republic; Denmark; Finland; Germany; Hungary; India; Iran; Israel; Italy; Japan; Netherlands; Poland; Russia; Singapore; Slovenia; South Korea; Spain; Sweden; Switzerland; Taiwan; Thailand; United Kingdom; United States.**
RIKEN	**Bank(Japan)** www.riken.jp/en/	**Japan[*1]**
eagle-i	**Registry(U.S.)** www.eagle-i.net	**United States[*2]**
hPSCreg	**Registry(EU)** hpscreg.eu	**Australia; Austria; Belgium; Brazil; Canada; China; Czech Republic; Denmark; Finland; France; Germany; Hungary; India; Iran; Ireland; Israel; Italy; Japan; Luxembourg, Netherlands; Portugal; Norway; Qatar; Russia; Singapore; Slovenia; South Korea; Spain; Sweden; Switzerland; Taiwan; Thailand; Turkey; United Kingdom; United States.**

ICSCB

1. Related organization list: https://www.amed.go.jp/content/000043772.pdf
2. Participating institutions: https://www.eagle-i.net/about/participating-institutions/

As of March 26, 2020

Fig4 Workflow

Fig5 Reference table

A

Keyword search

SKIP

- cell id
- stemcell_id
- cell line name
- research grade
- establisher name
- establisher organization
- pubmed ID
- donor sex
- donor race
- disease name
- cell type
- organ/tissue of origin of source cell
- in vivo differentiation assay
- in vitro differentiation
- cell morphology
- pluripotent marker
- karyotype assay
- CNV detail
- remaining vector detection test assay
- whole genome detail
- stem cell transcriptome analysis detail
- epigenetics detail

eagle-i

- cell id
- cell line label
- cell line provider
- sex
- ethnicity
- diagnosed disease
- cell line type
- cell line URL

hPSCreg

- source organism
- race
- cell lineage
- health status
- shogoin cell id
- stem cell id
- stem cell name
- produced by
- distributor
- publication
- gender
- race
- health status
- source cell type
- source cell description
- origin of source cell

Riken BRC

- cell name
- cell ID
- description
- original website
- originator
- depositor
- taxon
- depiction
- common name
- cell grouping
- reference
- derived from
- gender
- race
- country
- disease
- age

B

 Integrated Collection of Stem Cell Bank data by MIACARM

Data source	Source cell											
	Stem cell production											
	Stem cell general identification							Donor identification			Source cell identification	
	Stem cell ID	Stem cell name	Stem cell type	Cell grade	Produced by	Provider/ distributor	Reference publication	Gender of donor	Ethnicity of donor	Health status ofdonor	Source cell type	Organ/ tissue of origin of source cell
SKIP	SKIP000001	201B7	iPS Cell	Research Grade	Yamanaka Shinya.	Center for iPS Cell Research and Application, Kyoto University	18035408 -- 23300777 -- 27073925 -- 27161380	Female	Caucasian			Skin

CellLine:Transgene:Retrovirus, pMXs-Oct3/4, -Sox2, -Klf4, -c-Myc, pLenti6/UbC/V5-DEST, mouse Slc7a1

B/R*	Stem cell bank or registry	Country	Website	Number of cell lines
B	BLCB	Spain	http://www.cmrb.eu/	79
R	hPSCreg	Germany	https://hpscreg.eu/	3099
R	HipSci	United Kingdom	http://www.hipsci.org/	799
B	U.K. Stem Cell Bank	United Kingdom	https://www.nibsc.org/	36
B	EBiSC	Germany	https://ebisc.org/	897
B/R	CIRM / FUJIFILM	United States	https://fujifilmcdi.com/the-cirm-ipsc-bank/	1545
B	Harvard Stem Cell Institute	United States	http://stemcelldistribution.harvard.edu/	40
B	NYSCF	United States	https://nyscf.org/	63
B	NINDS Human Cell and Data Repository	United States	https://bioq.nindsgenetics.org/	377
B	WiCell Research Institute	United States	https://www.wicell.org/	1505
B/R	eagle-i	United States	https://www.eagle-i.net/	3548
B/R	RIKEN BRC	Japan	https://en.brc.riken.jp/	3545
R	SKIP	Japan	https://skip.stemcellinformatics.org/	5615
B	JCRB	Japan	https://cellbank.nibiohn.go.jp/	16
B	Taiwan Human Disease iPSC Service Consortium	Taiwan	https://catalog.bcrc.firdi.org.tw/Welcome/	89
B	National Stem Cell Bank of Korea	Korea	http://kscr.nih.go.kr/nscb/en/kscr/index.do/	172

* B, bank; R, registry

Table 1. Stem cell banks and registries worldwide (as of March 26, 2020)

MIACARM module	ICSCB term	hPSCreg	SKIP	RIKEN BRC	eagle-i
Stem cell general identification	Stem cell ID	stem cell id	stem cell id	CellID	cell line label
	Stem cell name	stem cell name	cell line name	CellName	cell line label
	Stem cell type	N.A.	cell type	cell grouping	cell line type
	Cell grade	N.A.	research grade	N.A.	N.A.
	Produced by	produced by	establisher name	originator	N.A.
	Provider/ distributor	distributor	establisher organization	depositor	cell line provider
	Reference publication	publication	pubmed ID	reference	N.A.
Donor identification	Gender of donor	gender	donor sex	gender	sex
	Ethnicity of donor	race	donor race	race	ethnicity
	Health status	health status	disease name	disease	diagnosed disease
Source cell identification	Source cell type	source cell type	N.A.	N.A.	N.A.
	Organ/tissue of origin of source cell	origin of source cell	organ/tissue of origin of source cell	N.A.	N.A.

N.A., not available.

Table 2. Cross-reference table for integration of four databases according to MIACARM module (as of March 26, 2020).

SUPPLEMENTAL INFORMATION

Integrated Collection of Stem Cell Bank data, a

data portal for standardized stem cell

information

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SUPPLEMENTAL FIGURES

Fig S1. Details of cell line types collected by eagle-i, RIKEN BRC, SKIP, and

hPSCreg (as of March 26, 2020)**.** (A) eagle-i, (B) RIKEN BRC, (C) SKIP, and (D)

hPSCreg

Fig S2. **Details of countries that have established cell lines in hPSCreg** (as of March

26, 2020)**.**

Fig S3. Details of countries that have established cell lines in SKIP (as of March 26,

2020)**.**

21   **Fig. S1**

23 **Fig. S2**

hPSCreg

Fig. S3

SKIP

SUPPLEMENTAL TABLES

Table S1. Related to Figure 5: List of full information of ICSCB as of March 26,

2020.

Table S2. Related to Figure 5A and Figure S1: List of cell line types across all four

databases (as of March 26, 2020)**.**

Table S3. Related to Figure 5B: Statistics of healthy/diseased cell lines in ICSCB

(as of March 26, 2020)**.**

Table S4. Related to Figure 5C: Statistics of cell line types based on country (as of

March 26, 2020)**.**

Table S5. Related to Figure 5D: Statistics of diseased cell lines based on disease

category (as of March 26, 2020)**.**

EXPERIMENTAL PROCEDURES

Generation of Fig. 1

Among all the databases, SKIP and hPSCreg provided details of countries from which

data were acquired. For SKIP, this information was provided on its homepage

(skip.stemcellinformatics.org/en/). For hPSCreg, country information for every cell line

could be accessed from its homepage (https://hpscreg.eu/) by clicking "find by

location".

Generation of Fig. 5

Full information data were directly downloaded from ICSCB results page (**Table S1**)

and filtered according to the following criteria: (A) stem cell type (**Table S2**); (B)

health/disease status (**Table S3**); (C) country (**Table S4**); and (D) disease (**Table S5**).

Disease categories were determined by search results with keywords under the "Disease

Category" in NCBI MeSH page (https://www.ncbi.nlm.nih.gov/mesh). For example,

searching with keywords of "Parkinson disease" will lead to the MeSH term "Nervous

57   System Diseases" under the "Disease Category". Pie charts and bar graphs were

58   produced by R (graph.r) using the package "plotly".

Table S1

Table S2

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