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Original Article

# Overview of the BioBank Japan Project: Study design and profile

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## ABSTRACT

*Background:* The BioBank Japan (BBJ) Project was launched in 2003 with the aim of providing evidence for the implementation of personalized medicine by constructing a large, patient-based biobank (BBJ). This report describes the study design and profile of BBJ participants who were registered during the first 5-year period of the project.

*Methods:* The BBJ is a registry of patients diagnosed with any of 47 target common diseases. Patients were enrolled at 12 cooperative medical institutes all over Japan from June 2003 to March 2008. Clinical information was collected annually via interviews and medical record reviews until 2013. We collected DNA from all participants at baseline and collected annual serum samples until 2013. In addition, we followed patients who reported a history of 32 of the 47 target diseases to collect survival data, including cause of death.

*Results*: During the 5-year period, 200,000 participants were registered in the study. The total number of cases was 291,274 at baseline. Baseline data for 199,982 participants (53.1% male) were available for analysis. The average age at entry was 62.7 years for men and 61.5 years for women. Follow-up surveys were performed for participants with any of 32 diseases, and survival time data for 141,612 participants were available for analysis.

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<sup>u</sup> Hospital Group members are listed in Appendix A.

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*Conclusions:* The BBJ Project has constructed the infrastructure for genomic research for various common diseases. This clinical information, coupled with genomic data, will provide important clues for the implementation of personalized medicine.

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## Introduction

With the rapid advancement of human genetic research, researchers have found many genetic variations that contribute to disease susceptibility and drug responses.<sup>1–3</sup> Based on these achievements, personalized medicine is expected to provide optimal medical treatment by taking into account individual genetic makeup.<sup>4,5</sup>

To better achieve this goal, the Japanese Ministry of Education, Culture, Sports, Science and Technology launched the BioBank Japan (BBJ) Project in 2003. This project is being conducted in three 5-year periods. In the first period (April 2003 to March 2008), the project constructed a large, patient-based biobank, referred to as the BBJ, as the basic infrastructure for genetic research for common diseases; this was accomplished through the collection of clinical information and biological samples related to 47 target diseases and with the cooperation of 12 Japanese medical institutes. In the second period (April 2008 to March 2013), the project conducted various genomic investigations and identified genetic variations related to disease susceptibility and drug responses using a genome-wide association study approach.<sup>6</sup> In the third period (April 2013 to March 2018), the project will expand the BBJ by enrolling new participants with 38 target diseases, starting sequence-based genomic analyses, and constructing a tissue bank.

Ultimately, the BBJ aims to (1) discover the genes that contribute to various diseases and those related to the efficacy or adverse reactions of drugs, (2) to provide useful information regarding molecular targets for the evidence-based development of new drugs and/or diagnostic tools, (3) to examine interactions between genetic



and treatment factors related to the progression of diseases, and (4) to provide important medical information that can be applied to the implementation of personalized medicine.<sup>7</sup> This project is jointly managed by The Institute of Medicine of The University of Tokyo and the RIKEN Center for Integrative Medical Sciences.

This paper provides an overview of the BBJ Project as well as a profile of the BBJ participants who were registered in the first 5-year period of the project.

# Methods

## Study participants

The BBJ is a multi-institutional hospital-based registry that was initially designed to focus on the use of human genetic research. Therefore, this project registered not only patients with newly developed diseases (incident cases) but also patients who were diagnosed and treated before starting the project (prevalent cases). Project participants were recruited between June 2003 and March 2008 from 66 hospitals, which consisted of 12 cooperating medical institutions located throughout Japan (Fig. 1). Attending physicians identified patients with any of 47 target diseases. Before enrollment, patients received a detailed explanation regarding the project from expert, independent medical coordinators who were specifically trained for this project. Biological samples and clinical information were collected and anonymized on-site at the cooperating hospitals. All study participants had been diagnosed with one or more of 47 target diseases, which are listed in Table 2. These target diseases were selected by clinical importance based on morbidity or mortality in Japan through discussion with cooperating medical institutions. Diagnoses of these diseases were based on the physicians' diagnoses at cooperating hospitals. We excluded patients who had received a bone marrow transplant and those who were not of East Asian descent.

Clinical Information collected during the annual BioBank Japan survey.

Categories	Classifications
Common items	Basic clinical Information
	Current drug use
	History of adverse drug events
Laboratory examination items	Malignant tumors
	Cerebral diseases
	Respiratory diseases
	Cardiovascular diseases
	Liver diseases
	Urologic diseases
	Metabolic diseases
	Endocrine diseases
	Connective tissue diseases
	Allergic diseases
	Dermatological diseases
	Gynecological diseases
	Pediatric diseases
	Ophthalmologic diseases
	Dental diseases
Disease-specific items	_

Fig. 1. Geographical distribution of cooperating hospitals.

	-
Table	2

Number of cases of 47 diseases and disease durations at the time of entry in the BioBank Japan Project.

serum     serum     entry (interquent) e	Disease group	Disease name	Number of cases (with serum)		Median disease duration at entry (interquartile range,	
Malignant tumors     Lung carcer Esophageal cancer     37/9     (3777)     0.7     (0.2–2.9)       Gastric cancer     5322     (6151)     1.0     (0.2–3.4)       Gastric cancer     6532     (6754)     1.0     (0.2–3.4)       Liver cancer     6532     (6754)     1.0     (0.2–3.4)       Jeancreas cancer     1924     (1922)     1.2     (0.3–3.4)       Protostac cancer     1934     (1922)     1.2     (0.3–3.4)       Protostac cancer     1934     (1922)     1.2     (0.3–3.4)       Protostac cancer     5066     (5065)     1.0     (0.2–2.6)       Derival cancer     128     (1218)     1.8     (0.2–3.4)       Overan cancer     1363     (6365)     1.0     (0.3–3.4)       Uterine cancer     1028     (1202)     1.5     (0.4–4.3)       Uterine cancer     2033     (2275)     5.6     (1.7–13.4)       Respiratory diseases     2033     (2275)     5.6     (1.7–13.4)       Respiratory diseases     2030     (2275)						
Malignant tumors     Lung cancer     3779     (3777)     0.7     (0.2-2.8)       Gastric cancer     6321     (6316)     1.0     (0.2-2.8)       Gastric cancer     6322     (6316)     1.0     (0.2-3.8)       Liver cancer     1924     (1922)     1.2     (0.3-3.4)       Liver cancer     1924     (1922)     1.2     (0.3-3.4)       Pracess cancer     5066     (5065)     1.0     (0.3-2.8)       Breast cancer     6316     (5365)     0.8     (0.2-3.6)       Uterine cancer     1266     (5065)     1.0     (0.3-2.8)       Breast cancer     1266     (1026)     1.5     (0.4-4.3)       Ovarian cancer     1307     (1652)     2.2     (0.4-5.6)       Cerebral diseases     Cerebral infarction     15.534     (1652)     2.2     (0.4-5.6)       Cardiovascular diseases     Bronchial asthma     8700     (8642)     9.0     (3.0-20.0)       Cardiovascular diseases     Corboral infarction     13.272     (13.270)     3.8     (0.7-5.4) <th></th> <th></th> <th></th> <th></th> <th>years)</th> <th></th>					years)	
n     1291     (1290)     0.4     (0.2-80)       Gastric cancer     622     (631)     1.0     (0.2-40)       Colorectal cancer     6759     (6754)     1.0     (0.2-34)       Iver cancer     392     (393)     0.4     (0.1-1.5)       Calibidade/(bolangioacrinoma     392     (393)     0.4     (0.2-2.1)       Porstate cancer     5066     (5065)     1.0     (0.2-3.6)       Cervical cancer     5066     (5065)     1.0     (0.2-3.6)       Ovarian cancer     1218     (128)     1.8     (0.4-3.6)       Uterine cancer     1206     (1020)     1.5     (0.4-4.4)       Ovarian cancer     888     (18.52)     2.2     (0.4-5.1)       Erebral disease     Cerebral infarction     16.534     (16.52)     2.2     (0.4-5.1)       Pulmonary tuberculosis     863     (862)     NA     (1.0-80)       Interstitial lung disease/Pulmonary disease?     863     (862)     NA     (1.0-70)       Cardiovascular diseases     1000     1701	Malignant tumors	Lung cancer	3779	(3777)	0.7	(0.2 - 2.9)
Gatric cancerG322(G316)1.0(0.2-4.0)Colorectal cancer1924(1922)1.2(0.3-3.4)Parcess cancer392(393)0.5(0.2-3.4)Parcess cancer396(506)1.0(0.3-2.8)Prosta cancer636(506)1.0(0.3-2.8)Parcess cancer6336(6336)0.8(0.2-3.6)Prosta cancer6336(6336)0.8(0.3-2.8)Cervical cancer1026(1025)1.5(0.4-4.5)Uterize cancer1026(1025)1.5(0.4-4.5)Ovrain cancer1307(1303)2.4(0.9-5.1)Cerebral aneuryam2710(2709)N/A(27.1)Cerebral aneuryam2710(2709)N/A(1.1-3.4)Palmonary tuberculosis863(662)9.0(1.0-8.0)Interstitial lung disease <sup>1</sup> 2714(2711)3.0(1.0-8.0)Interstitial lung disease <sup>1</sup> 15.912(1.32.70)3.6(1.7-3.4)Stable angina*4330(4324)2.6(0.5-4.5)Urologic disease2683(2679)N/A(1.0-8.0)Interstitial lung disease <sup>1</sup> 15.912(1.32.70)3.6(1.0-7.9)Arriythmia*15.912(1.505)3.7(1.1-8.3)Liver disease2683(2679)N/A(2.0-1.20)Distable angina*4330(336)(30(2.0-1.20)Arriythmia*15.912(1.505)3.7(1.1-8.3) <td></td> <td>Esophageal cancer</td> <td>1291</td> <td>(1290)</td> <td>0.4</td> <td>(0.2 - 2.8)</td>		Esophageal cancer	1291	(1290)	0.4	(0.2 - 2.8)
closectal cancer6739(6754)1.0(0.2-3.4)Liver cancer1924(1322)1.2(3.3-3.3)Gallbackler(chalagiacarinoma192(393)0.5(0.2-2.1)Porstate cancer6066(5065)1.0(0.2-3.6)Callbackler(chalagiacarinoma6036(6336)0.8(0.2-3.6)Devistate cancer6336(6336)1.8(0.4-3.6)Cervical cancer1218(118)1.8(0.4-3.6)Ovaria cancer888(888)1.8(0.4-3.6)Ovaria cancer6334(16522)2.2(0.4-5.6)Cerebral infarction16.334(16522)2.2(0.4-5.6)Cerebral infarction6334(16522)9.0(0.4-3.6)Pilpepsy203(275)5.6(1.7-13.4)Respiratory diseasesCerebral infarction13.272(13.270)3.8(0.7-8.7)Cardiovascular diseasesMyocardial infarction13.272(13.270)3.8(0.7-8.7)Unstable angina"4380(8424)2.6(-5.6.4)(1.6-7.9)Arrhythmia"15.912(15.905)3.7(1.1-8.9)Liver diseases2519(269)N/A(-1.6-8.9)Uradie infarction13.272(13.270)3.8(0.7-8.7)Uradie infarction13.272(13.270)3.8(0.7-8.7)Uradie angina"14.807(14.800)3.6(1.0-7.9)Arrhythmia"15.912(15.905)3.7(1.1-8.9)		Gastric cancer	6322	(6316)	1.0	(0.2 - 4.0)
Liver cancer     1924     (1922)     1.2     (0.3-3.3)       Pancross cancer     392     (393)     0.5     (0.2-3.1)       Prostate cancer     0366     (5065)     1.0     (0.3-2.8)       Breast cancer     6336     (6336)     0.8     (0.2-3.6)       Cervical cancer     1026     (1026)     1.5     (0.4-4.4)       Ovarian cancer     1026     (1026)     1.5     (0.4-4.4)       Ovarian cancer     1026     (10632)     2.2     (0.4-5.6)       Cerebral infarction     16574     (1632)     2.2     (0.4-5.6)       Erebral aneurysm     2710     (2709)     NA     (1.7-13.4)       Attributer culosis     863     (862)     NO     (1.0-7.0)       Attributer culosis     863     (862)     NO     (1.0-7.0)       Attributer culosis     863     (864)     3.0     (1.0-7.0)       Attributer culosis     864     (844)     3.0     (1.0-8.3)       Attributer culosis     810     (812,70)     3.8     (1.0-7.0) </td <td></td> <td>Colorectal cancer</td> <td>6759</td> <td>(6754)</td> <td>1.0</td> <td>(0.2 - 3.4)</td>		Colorectal cancer	6759	(6754)	1.0	(0.2 - 3.4)
Pancreas cancer     92     (392)     0.4     (0.1-5)       Gallbadder(cholangicarcinoma     922     (393)     0.5     (0.2-2.1)       Prostate cancer     5066     (5065)     1.0     (0.2-2.5)       Breast cancer     5066     (5065)     1.0     (0.2-2.6)       Cervical cancer     1218     (1218)     1.8     (0.4-5.3)       Utrine cancer     1026     (1026)     1.5     (0.4-4.4)       Ovarian cancer     888     (888)     1.8     (0.5-5.1)       Cerebral infarction     (5.344     (15.22)     2.2     (0.4-5.3)       Cerebral infarction     (5.344     (15.22)     2.2     (0.4-5.3)       Pilpionsny tuberculois     863     (862)     NA     (0.4-5.3)       Cardiovascular diseases     0.8     (804)     3.0     (1.0-5.0)       Cardiovascular diseases     0.8     (804)     3.0     (1.0-7.9)       Arriby thimia'     1.512     (1.505)     3.7     (1.1-8.9)       Liver diseases     Myocaridia infarction     1.3272		Liver cancer	1924	(1922)	1.2	(0.3 - 3.3)
calibiadder/Cholangiocarcinoma     392     (393)     0.5     (22-21)       Prostate cancer     6366     (5065)     1.0     (32-28)       Breast cancer     6366     (6365)     0.8     (02-31)       Cervical cancer     1218     (1218)     1.8     (02-31)       Uterine cancer     0266     (1026)     1.5     (04-44)       Ovarian cancer     888     (888)     1.8     (02-4)       Cerebral infarction     16,534     (16522)     2.2     (04-53)       Cerebral aneurysm     2710     (2709)     N/A     (10-70)       Espiratory diseases     Bronchial asthma     8700     (8642)     9.0     (30-200)       Pulmonary tuberculosis     863     (864)     3.0     (10-7.0)       Aradyoradia infarction     13,272     (13,270)     3.8     (07-8.7)       Aradyoradia infarction     13,272     (13,270)     3.8     (07-8.7)       Cardiovascular diseases     Myooradrali infarction     13,272     (13,270)     3.8     (07-8.7)       Juritobia sint		Pancreas cancer	392	(392)	0.4	(0.1 - 1.5)
Prostate cancer5066(5005)1.0 $(0.3-2.6)$ Brast Cancer6356(536)0.8 $(0.2-3.6)$ Cervical cancer1218(1218)1.8 $(0.4-5.3)$ Uterine cancer026(1026)1.5 $(0.4-4.4)$ Ovarian cancer888(888)1.8 $(0.5-4.9)$ Cerebral discasesCerebral infarction16.534(16.522)2.2 $(0.4-5.6)$ Cerebral aneurysm2710(2709)N/A-Epliepsy2303(2275)5.6 $(1.7-13.4)$ Respiratory diseasesBronchial asthma8700(8642)9.0(30-20.0)Pulmonary tuberculosis863(862)N/A-Cardiovascular diseasesMycardial infarction13.272(13.270)3.8 $(0.7-8.7)$ Unstable angina*4330(4324)2.6 $(0.5-6.4)$ -Arrhythmia*15.912(15.905)3.7 $(1.1-8.3)$ Heart failure*7610(7601)1.9 $(0.4-5.0)$ Liver diseasesChronic hepatitis E81346(1345)N/AUrologic diseasesChronic hepatitis E81346(1345)N/AUrologic diseasesCrave' disease2233(2579)N/AUrologic diseasesRemutidi affritis4139(4139)N/ALiver dires syndrome1056(1007)N/A-Liver dires syndrome1056(1007)N/A-Liver dires sesReturnedid affritis4139<		Gallbladder/Cholangiocarcinoma	392	(393)	0.5	(0.2 - 2.1)
Breast cancer     636     (636)     0.8     (02-3.6)       Cerebral cancer     1218     (1218)     128     (024)       Uterine cancer     1026     (1026)     1.5     (04-4.3)       Ovarian cancer     888     (880)     1.8     (05-4.3)       Cerebral infarction     1307     (1303)     2.4     (0.9-5.1)       Cerebral infarction     15.01     (15.522)     2.2     (0.4-5.6)       Cerebral infarction     15.01     (2709)     NIA     (1.0-8.0)       Bespiratory diseases     Bronchial astman     8700     (8642)     9.0     (3.0-20.0)       Pulmonary tuberculosis     863     (862)     NIA     (1.0-8.0)       Interstitial lung disease/humonary fibrosis     808     (804)     3.0     (1.0-7.0)       Cardiovascular diseases     Interstitial ing disease/humonary fibrosis     1330     (424)     2.6     (0.5-6.4)       Unorido expartitis A     15.912     (15.905)     3.7     (1.1-8.3)       Heart failure <sup>n</sup> 15.912     (15.905)     3.7     (1.1-8.3)		Prostate cancer	5066	(5065)	1.0	(0.3-2.8)
Cervical cancer128(1218)1.8(04-5.3)Urentine cancer1026(1026)1.5(04-4.4)Ovarian cancer888(880)1.8(05-4.9)Hematopoietic tumor1307(1103)2.4(0.9-5.1)Cerebral infarction16.534(16.522)2.2(0.4-5.6)Cerebral infarction16.534(16.523)2.6(1.7-13.4)Respiratory diseasesCerebral infarction863(862)9.0(3.0-20.0)Munoary tuberculosis863(862)9.0(1.0-7.0)Cardiovascular diseasesMycardial infarction13.272(13.270)3.8(0.7-8.7)Cardiovascular diseasesMycardial infarction13.272(13.270)3.8(0.7-8.7)Cardiovascular diseasesMycardial infarction13.272(13.270)3.8(0.7-8.7)Cardiovascular diseasesMycardial infarction13.272(13.270)3.8(0.7-8.7)Arrhythmia*15.912(15.905)3.7(1.1-8.3)Arrhythmia*15.912(15.905)3.7(1.1-8.3)Herri failure*7610(7601)1.9(0.4-7.9)Arrhythmia*13.646(1345)N/A(1.0-7.9)Liver diseasesChronic hepatitis C818(3817)N/ALiver diseasesNephrotic syndrome1056(1007)N/ALiver diseasesReinfailure*39.697(3.086)6.0(2.0-12.0)Diabetes mellitus*39.697(3.086) </td <td></td> <td>Breast cancer</td> <td>6336</td> <td>(6336)</td> <td>0.8</td> <td>(0.2 - 3.6)</td>		Breast cancer	6336	(6336)	0.8	(0.2 - 3.6)
Uterine cancer     1026     102655     102655     102655		Cervical cancer	1218	(1218)	1.8	(0.4-5.3)
Ovarian cancer88(88)1.8(05-4.9)Greebral infarction1307(1303)2.4(09-5.1)Cerebral infarction16.534(16.522)2.2(04-5.6)Cerebral aneurysm2710(2709)N/ARespiratory diseasesBronchial asthma8700(8642)9.0(30-20.0)Mumoary tuberculosis883(862)N/A(10-8.0)Cardiovascular diseasesMumoary tuberculosis808(804)3.0(10-7.0)Cardiovascular diseasesMyocardial infarction13.272(13.270)3.8(07-8.7)Myocardial infarction43.207(14.800)3.6(1.0-7.9)Arritythmia'15.912(15.905)3.7(1.1-8.3)Herstitial lung disease/Pulmonary disease2683(2679)N/ALiver diseasesPeripheral arterial diseases2683(2679)N/ALiver diseasesNonic hepatitis B1346(1345)N/ALiver diseasesNephrotic syndrome1056(1007)N/AMetabolic diseasesOsteoporosis6743(6739)N/AMetabolic diseasesGarves' disease2338(2866)16.0Connective tissue diseasesHay fever555(5645)N/APerdidir diseasesHay fever333(275)N/ADetorine diseasesHay fever333(275)N/AConnective tissue diseasesHay fever555(5645)N/APerdidir diseasesH		Uterine cancer	1026	(1026)	1.5	(0.4 - 4.4)
Cerebral diseasesHematopoleic tumor1307(1303)2.4(0.9–5.1)Cerebral aneurysm2710(2709)N/AEpilepsy2303(275)5.6(1.7–13.4)Respiratory diseasesBronchial asthma8700(8642)9.0(3.0–20.0)Pulmonary tuberculosis863(862)N/A(1.0–8.0)Cardiovascular diseases13.272(13.270)3.8(1.0–7.0)Cardiovascular diseasesMyocardial infarction13.272(13.270)3.8(0.7–8.7)Unstable angina*4330(4324)2.6(0.5–6.4)Arrhythmia*15.912(15.905)3.7(1.1–8.3)Heart fallure*7610(7601)1.9(0.4–5.4)Peripheral arterial diseases2683(2679)N/ALiver diseasesChronic hepatitis B1346(1345)N/ALiver diseasesOscoporosis6743(6739)N/AUrologic diseasesRephrotic syndrome1056(1007)N/AUrologic diseasesHay fever558(5645)N/ADetermating*39.697(39.686)6.0(2.0–12.0)AdheresGaves' disease2323(2322)N/AUrologic diseasesHay fever558(5645)N/ADetermatiogic diseasesHay fever558(5645)N/AConnective tissue diseasesHay fever555(5645)N/AConnective tissue diseasesHay fever5563(5645)		Ovarian cancer	888	(888)	1.8	(0.5 - 4.9)
Cerebral diseases     Cerebral aneurysm     16,534     16,522)     2.2     (0.4-5.6)       Cerebral aneurysm     2710     (2709)     N/A       Respiratory diseases     Bronchial astma     8700     (8642)     9.0     (3.0-20.0)       Mulmonary tuberculosis     863     (862)     N/A     (2771)     3.0     (1.0-8.0)       Cardiovascular diseases     Myocardial infarction     13,272     (13,270)     3.8     (0.7-8.7)       Unstable angina"     14,800     (14,800)     3.6     (1.0-7.9)       Arrhythmia"     14,801     (14,800)     3.6     (1.0-7.9)       Arrhythmia"     14,807     (14,800)     N/A     (1.0-8.0)       Liver diseases     Chronic hepatitis S     S819     (5817)		Hematopoietic tumor	1307	(1303)	2.4	(0.9 - 5.1)
Cerebral aneurysm     2710     (2709)     N/A       Epilepsy     2303     (2275)     5.6     (1.7–134)       Respiratory diseases     8700     (8642)     9.0     (3.0–20.0)       Pulmonary tuberculosis     863     (862)     N/A       Cardiovascular diseases     Interstitial lung disease/Pulmonary disease     2774     (2771)     3.0     (1.0–8.0)       Cardiovascular diseases     Myocardial infarction     13,272     (13,270)     3.8     (0.7–8.7)       Cardiovascular diseases     Myocardial infarction     14,807     (14,800)     3.6     (1.0–7.9)       Arrhythmia <sup>4</sup> 15,912     (15,905)     3.7     (1.1–8.0)       Heart failure <sup>a</sup> 7610     (7601)     1.9     (0.4–5.4)       Iver dirbasis     7610     (7601)     N/A     -       Liver dirbasis     1346     (1345)     N/A       Urologic diseases     Nephrotic syndrome     1056     (1007)     N/A       Urologic diseases     Repurption     33,0997     (39,686)     6.0     (2.0–12.0)	Cerebral diseases	Cerebral infarction	16,534	(16,522)	2.2	(0.4 - 5.6)
Epilepsy2303 $(2275)$ 5.6 $(1,7-13.4)$ Respiratory diseasesBronchial asthma8700 $(842)$ 9.0 $(3.0-20.0)$ Pulmonary tuberculosis863 $(862)$ N/AChronic obstructive pulmonary disease*2774 $(2771)$ 3.0 $(1.0-8.0)$ Cardiovascular diseasesMyocardial infarction13.272 $(13.270)$ 3.8 $(0.7-8.7)$ Unstable angina*14.807 $(14.800)$ 3.6 $(1.0-7.0)$ Arrhythmia*15.912 $(15.905)$ 3.7 $(1.1-8.3)$ Heart failure*7610 $(7601)$ 1.9 $(0.4-5.4)$ Liver diseases2683 $(2679)$ N/A $(1.0-7.0)$ Liver diseases2683 $(2679)$ N/A $(1.0-7.0)$ Liver diseases2519 $(2509)$ N/A $(1.0-7.0)$ Urologic diseasesNephrotic syndrome1056 $(1007)$ N/AUrologic diseasesRespirating*39.697 $(39.686)$ 6.0 $(2.0-12.0)$ Diabetes mellitus*39.697 $(39.686)$ 6.0 $(2.0-12.0)$ Diabetes mellitus*39.697 $(39.686)$ $(5.0-25.0)$ Arby dermatifis*4139 $(4139)$ $7.7$ $(2.6-15.3)$ Allergic diseasesRheumatoid arthritis4132 $(37.8)$ $(3.0)$ $(1.0-7.0)$ Dermatologic diseasesRheumatoid arthritis809 $(808)$ N/A $(2.0-12.0)$ Distes mellitus*39.697 $(39.686)$ $(5.0)$ $(2.0-12.0)$ Distes mellitus*		Cerebral aneurysm	2710	(2709)	N/A	· · · ·
Respiratory diseases     Bronchial asthma Pulmonary tuberculosis     8700     (8642)     9.0     (3.0-20.0)       Pulmonary tuberculosis     863     (862)     N/A       Cardiovascular diseases     10ronic obstructive pulmonary fibrosis     863     (862)     N/A       Cardiovascular diseases     Myocardial infraction     13.272     (13.270)     3.8     (0.7-8.7)       Cardiovascular diseases     Myocardial infraction     14.807     (14.800)     3.6     (1.0-7.9)       Cardiovascular diseases     Peripheral arterial diseases     7610     (7601)     1.9     (0.4-5.4)       Liver diseases     Chronic hepatitis B     1346     (1345)     N/A       Liver diseases     Chronic hepatitis B     1346     (1345)     N/A       Urologic diseases     Chronic hepatitis B     1346     (137)     N/A       Urologic diseases     Osteoporosis     6307     (6306)     N/A       Urologic diseases     Graves' disease     2323     (2322)     N/A       Diabetes mellitus <sup>6</sup> 398     (388)     (808)     N/A <t< td=""><td></td><td>Epilepsy</td><td>2303</td><td>(2275)</td><td>5.6</td><td>(1.7 - 13.4)</td></t<>		Epilepsy	2303	(2275)	5.6	(1.7 - 13.4)
Pulmonary tuberculosis863(862)N/AChronic obstructive pulmonary disease <sup>1</sup> 2774(2771)3.0 $(1.0-7.0)$ Cardiovascular diseasesMyocardial infarction13.272 $(13.270)$ 3.8 $(0.7-8.7)$ Unstable argina <sup>1</sup> 4330(4324)2.6 $(0.5-6.4)$ Stable angina <sup>1</sup> 14.807 $(14.800)$ 3.6 $(1.0-7.0)$ Arrhythmia <sup>4</sup> 15.912 $(15.905)$ 3.7 $(1.1-8.3)$ Heart failure <sup>4</sup> 7610(7601)1.9 $(0.4-5.4)$ Veripheral arterial diseases2683(2679)N/ALiver diseasesChronic hepatitis B1346 $(1345)$ N/ALiver diseasesChronic hepatitis C5819 $(5817)$ N/AUrologic diseasesNephrotic syndrome1056 $(1007)$ N/AUrologic diseasesOsteoprosis6743 $(6739)$ N/ADiabetes mellitus <sup>3</sup> 39.607(39.686)6.0 $(2.0-12.0)$ Indectrine diseasesGraver disease2323 $(2322)$ N/AConnective diseasesHay fever5658 $(5645)$ N/ADermatologic diseasesDrug eruption585 $(586)$ N/AConnective diseasesFebrile seizure333 $(275)$ N/APermatologic diseasesFebrile seizure333 $(275)$ N/ADermatologic diseasesFebrile seizure333 $(275)$ N/ADetratitis'Sause2338 $(3896)$ $(1.1-8.2)$ Ophthalmologic	Respiratory diseases	Bronchial asthma	8700	(8642)	9.0	(3.0 - 20.0)
Chronic obstructive pulmonary disease <sup>a</sup> 2774 $(2771)$ $3.0$ $(1.0-8.0)$ $(1.0-7.0)$ Cardiovascular diseasesInterstitial lung disease/Pulmonary fibrosis808 $(804)$ $3.0$ $(1.0-7.0)$ Cardiovascular diseasesMyocardial infarction $13.272$ $(13.270)$ $3.8$ $(0.7-8.7)$ Unstable angina <sup>a</sup> 4330 $(4324)$ $2.6$ $(0.5-6.4)$ Stable angina <sup>a</sup> 14.807 $(14,800)$ $3.6$ $(1.0-7.9)$ Arrhythmia <sup>a</sup> $15.912$ $(15.905)$ $3.7$ $(1.1-8.3)$ Heart failure <sup>a</sup> 7610 $(7601)$ $1.9$ $(0.4-5.4)$ Peripheral arterial diseases $2633$ $(2679)$ $N/A$ Liver dirbosis $2519$ $(5817)$ $N/A$ Liver dirbosis $2519$ $(5817)$ $N/A$ Urologic diseasesNephrotic syndrome $056$ $(1007)$ $N/A$ Metabolic diseasesOsteoprosis $6743$ $(6739)$ $N/A$ Diabetes mellitus <sup>b</sup> $39.697$ $(39.686)$ $6.0$ $(2.0-12.0)$ Dyslipidemia <sup>b</sup> $4139$ $(4139)$ $7.7$ $(2.6-15.3)$ Allergic diseasesHay fever $5658$ $(586)$ $N/A$ Dermatologic diseasesHay fever $5934$ $(5902)$ $N/A$ Perindenal trintisis $333$ $(275)$ $N/A$ Dermatologic diseasesHurotidriafica $39384$ $(886)$ $(182)$ Ophthalmologic diseasesFebrile seizure $333$ $(275)$ $N/A$ Detratologic diseases </td <td>····· · · · · · · · · · · · · · · · ·</td> <td>Pulmonary tuberculosis</td> <td>863</td> <td>(862)</td> <td>N/A</td> <td>()</td>	····· · · · · · · · · · · · · · · · ·	Pulmonary tuberculosis	863	(862)	N/A	()
Interstitial lung disease/Pulmonary fibrosis808 $(80^4)$ 3.0 $(1.0-7.0)$ Cardiovascular diseasesMyocardial infarction13.272 $(13.270)$ 3.8 $(0.7-8.7)$ Myocardial infarction13.272 $(13.270)$ 3.8 $(0.7-8.7)$ Instable angina*14.807 $(14.800)$ 3.6 $(1.0-7.9)$ Arrhythmia*15.912 $(15.905)$ 3.7 $(1.1-8.3)$ Heart failure*7610 $(7601)$ 1.9 $(0.4-5.4)$ Liver diseases2683 $(2679)$ N/A $(1.1-8.3)$ Liver diseasesChronic hepatitis B1346 $(1345)$ N/ALiver diseasesPeripheral arterial diseases2683 $(2509)$ N/ALiver diseasesOstoporosis2519 $(2509)$ N/AUrologic diseasesNephrotic syndrome1056 $(1007)$ N/AUrologic diseasesOstoporosis6743 $(6739)$ N/AMetabolic diseasesGrave' disease2323 $(2322)$ N/AConnective tissue diseasesHay fever5658 $(5645)$ N/ADermatologic diseasesHay fever5658 $(5645)$ N/AConnective tissue diseasesHeur faitofa809 $(808)$ N/AConnective tissue diseasesFebrile seizure333 $(275)$ N/ADermatologic diseasesFebrile seizure333 $(275)$ N/AConnective tissue diseasesFebrile seizure333 $(275)$ N/AOphthalmologic diseasesFebrile seizu		Chronic obstructive pulmonary disease <sup>a</sup>	2774	(2771)	3.0	(1.0 - 8.0)
Cardiovascular diseases     Myocardial infarction     13,272     (13,270)     3.8     (0,7-8,7)       Unstable angina <sup>a</sup> 4330     (4324)     2.6     (0,5-6,4)       Stable angina <sup>a</sup> 4330     (4324)     2.6     (0,5-6,4)       Stable angina <sup>a</sup> 14,807     (14,800)     3.6     (1,0-7.9)       Arrhythmia <sup>a</sup> 15,912     (15,905)     3.7     (1,1-8.3)       Heart failure <sup>a</sup> 7610     (7601)     1.9     (0,4-5.4)       Peripheral atterial diseases     2683     (2679)     N/A       Liver diseases     Chronic hepatitis B     1346     (1345)     N/A       Liver dirhosis     2519     (2509)     N/A     Urologic diseases     Nephrotic syndrome     1056     (1007)     N/A       Metabolic diseases     Nephrotic syndrome     39,697     (39,686)     6.0     (2,0-12.0)       Diabetes mellitus <sup>b</sup> 39,697     (39,686)     6.0     (2,0-12.0)       Diabetes mellitus <sup>b</sup> 39,697     (39,686)     6.0     (2,0-12.0)       Diabetes mellitus <sup>b</sup>		Interstitial lung disease/Pulmonary fibrosis	808	(804)	3.0	(1.0-7.0)
Unstable angina <sup>4</sup> 430 $(4324)^{\prime}$ 2.6 $(0.5-6.4)$ Stable angina <sup>4</sup> 14,807 $(14,800)$ 3.6 $(1.0-7.9)$ Arrhythmia <sup>4</sup> 15,912 $(15,905)$ 3.7 $(1.1-7.9)$ Heart failure <sup>8</sup> 7610(7601)1.9 $(0.4-5.4)$ Peripheral arterial diseases2683(2679)N/ALiver diseasesChronic hepatitis B1346 $(1345)$ N/ALiver cirrhosis2519 $(2509)$ N/AUrologic diseasesNephotic syndrome1056 $(1007)$ N/AUrologic diseasesOsteoporosis6743 $(6739)$ N/AMetabolic diseasesOsteoporosis6743 $(6739)$ N/ADiabetes mellitus <sup>10</sup> 39,697(39,686)6.0 $(1.0-7.0)$ Parterio diseasesRheumatoid arthritis4139 $(4139)$ $7.7$ $(2.6-15.3)$ Allergic diseasesHay fever5658 $(5645)$ N/ADermatologic diseasesHay fever5904 $(5902)$ N/AConnective tissue diseasesHeuratitis <sup>4</sup> 2938 $(2896)$ $16.0$ $(5.0-25.0)$ Keloid809(808)N/ACynecologic diseasesFehrile seizure333 $(275)$ N/APediatric diseasesFehrile seizure333 $(275)$ N/ADental diseasesFehrile seizure33898 $(3896)$ $(1.1-8.2)$ Ophthalmologic diseasesFeinel seizure33898 $(3896)$ $(1.00-1.7)$ Dental diseases <td>Cardiovascular diseases</td> <td>Mvocardial infarction</td> <td>13.272</td> <td>(13,270)</td> <td>3.8</td> <td>(0.7 - 8.7)</td>	Cardiovascular diseases	Mvocardial infarction	13.272	(13,270)	3.8	(0.7 - 8.7)
Stable angina <sup>4</sup> 14,807 $(14,80)$ 3.6 $(1.0-7.9)$ Arrhythmia <sup>4</sup> 15,912 $(15,905)$ 3.7 $(1.1-8.3)$ Heart failure <sup>4</sup> 7610 $(7601)$ 1.9 $(0.4-5.4)$ Peripheral arterial diseases2683 $(2679)$ N/ALiver diseasesChronic hepatitis B1346 $(1345)$ N/AUrologic diseasesChronic hepatitis C5819 $(5817)$ N/AUrologic diseasesNephrotic syndrome1056 $(1007)$ N/AUrologic diseasesOsteoprosis6743 $(6739)$ N/AMetabolic diseasesOsteoprosis6743 $(6739)$ N/AConnective tissue diseasesRheumatoid arthritis39,697 $(39,686)$ $6.0$ $(2.0-12.0)$ Dyslipidemia <sup>b</sup> 39,697 $(39,686)$ $6.0$ $(2.0-12.0)$ Dyslipidemia <sup>b</sup> 39,697 $(39,686)$ $6.0$ $(2.0-12.0)$ Diabetes mellitus <sup>b</sup> 39,697 $(39,686)$ $6.0$ $(2.0-12.0)$ Dyslipidemia <sup>b</sup> 39,697 $(39,686)$ $6.0$ $(2.0-12.0)$ Allergic diseasesHeumatoid arthritis $4139$ $7.7$ $(2.6-15.3)$ Allergic diseasesHay fever $5658$ $(586)$ N/AOpticalmologic diseasesDrug eruption $585$ $(586)$ N/APeriadogic diseasesUterine fibroid $5904$ $(5902)$ N/APediatric diseasesGerle esciure $333$ $(275)$ $N/A$ Pediatric diseasesGucoma $4755$ $(4733)$ </td <td></td> <td>Unstable angina<sup>a</sup></td> <td>4330</td> <td>(4324)</td> <td>2.6</td> <td>(0.5 - 6.4)</td>		Unstable angina <sup>a</sup>	4330	(4324)	2.6	(0.5 - 6.4)
Arrhythmia <sup>4</sup> 15,912(15,905)3.7(1.1-8.3)Heart failure <sup>4</sup> 7610(7601)1.9(0.4-5.4)Peripheral arterial diseases2683(2679)N/ALiver diseasesChronic hepatitis B1346(1345)N/AChronic hepatitis C5819(5817)N/ALiver cirrhosis2519(2509)N/AUrologic diseasesNephrotic syndrome1056(1007)N/AUrolithiasis6307(6306)N/AMetabolic diseasesOsteoporosis6743(6739)N/ADiabetes mellitus <sup>b</sup> 39,697(39,686)6.0(2.0-12.0)Dyslipidemia <sup>b</sup> 43,812(43,787)3.0(1.0-7.0)Endocrine diseasesGraves' disease2323(2322)N/AConnective tissue diseasesHay fever5658(5645)N/ADermatologic diseasesDrug eruption585(586)N/AArboic dermatitis <sup>a</sup> 2938(2896)16.0(5.0-25.0)Keloid809(808)N/AGynecologic diseasesUterine fibroid5904(5902)N/APediatric diseasesGerile seizure333(275)N/AOphthalmologic diseasesGaucoma4755(4753)3.6(1.1-8.2)Ophtal diseasesGaucoma4755(4753)3.6(1.1-8.2)Ophtal diseasesPeriodontitis3898(3896)0.1(0.0-1.7)Ophtal disea		Stable angina <sup>a</sup>	14.807	(14.800)	3.6	(1.0 - 7.9)
Hear failure <sup>a</sup> 7610(7601)1.9 $(0.4-5.4)$ Peripheral arterial diseases2683(2679)N/ALiver diseasesChronic hepatitis C5819(1345)N/ALiver cirrhosis2519(2509)N/AUrologic diseasesNephrotic syndrome1056(1007)N/AUrologic diseasesOsteoporosis6743(6739)N/AMetabolic diseasesOsteoporosis6743(6739)N/ADiabetes mellitus <sup>b</sup> 39,697(39,686)6.0(2.0-12.0)Dyslipidemia <sup>b</sup> 43,812(43,787)3.0(1.0-7.0)Endocrine diseasesGraves' disease2323(2322)N/AConnective tissue diseasesHay fever5658(5645)N/ADermatologic diseasesDrug eruption585(586)N/AAtopic dermatitis <sup>a</sup> 2938(2896)16.0(5.0-25.0)Keloid5904(5902)N/AConcetive tissue diseasesUtrine fibroid5904(5902)N/ADermatologic diseasesUtrine fibroid5904(5902)N/AEndometriosis1843(1843)N/APediatric diseasesGlaucoma4755(4753)3.6(1.1-8.2)Chronic heatitis20,002(19,988)1.5(0.2-5.4)Ophthalmologic diseasesPeriodontitis3898(3896)0.1(0.0-1.7)Dental diseasesPeriodontitis2898(271)4.0(2.1		Arrhythmia <sup>a</sup>	15.912	(15,905)	3.7	(1.1 - 8.3)
Peripheral arterial diseases2683 $(2679)$ N/ALiver diseasesChronic hepatitis B1346 $(1345)$ N/AChronic hepatitis C5819 $(5817)$ N/ALiver cirrhosis2519 $(2509)$ N/AUrologic diseasesNephrotic syndrome1056 $(1007)$ N/AMetabolic diseasesOsteoporosis6743 $(6739)$ N/ADiabetes mellitus <sup>b</sup> 39,697 $(39,686)$ $6.0$ $(2.0-12.0)$ Dyslipidemia <sup>b</sup> 43,812 $(43,787)$ $3.0$ $(1.0-7.0)$ Endocrine diseasesGraves' disease2323 $(2322)$ N/AConnective tissue diseasesReumatoid arthritis4139 $7.7$ $(2.6-15.3)$ Allergic diseasesHay fever5658 $(5645)$ N/ADermatologic diseasesDrug eruption585 $(586)$ N/AGynecologic diseasesUterine fibroid5904 $(5902)$ N/AEndometriosis1843 $(1843)$ N/A-Pediatric diseasesGaucoma4755 $(4753)$ $3.6$ $(1.1-8.2)$ Ophthalmologic diseasesGaucoma4755 $(771)$ $4.0$ $(2.1-6.9)$ Dental diseasesPeriodontitis3898 $(3896)$ $0.1$ $(0.0-1.7)$ Ophthalmologic diseasesGaucoma $(2.0-53)$ $(2.0-54)$ $(2.1-6.9)$ Dental diseasesPeriodontitis3898 $(3896)$ $0.1$ $(0.2-54)$ Dental diseasesPeriodontitis $(3902)$ $(1.9-75)$ <td< td=""><td></td><td>Heart failure<sup>a</sup></td><td>7610</td><td>(7601)</td><td>1.9</td><td>(0.4 - 5.4)</td></td<>		Heart failure <sup>a</sup>	7610	(7601)	1.9	(0.4 - 5.4)
Liver diseasesChronic hepatitis B1346(1345)N/AChronic hepatitis C5819(5817)N/ALiver cirrhosis2519(2509)N/AUrologic diseasesNephrotic syndrome1056(1007)N/AMetabolic diseasesOsteoporosis6743(6739)N/ADiabetes mellitus <sup>b</sup> 39,697(39,686)6.0(2.0-12.0)Dyslipidemia <sup>b</sup> 43,812(43,787)3.0(1.0-7.0)Endocrine diseasesGraves' disease2323(2322)N/AConnective tissue diseasesRheumatoid arthritis4139(4139)7.7(2.6-15.3)Allergic diseasesDrug eruption585(586)N/AAropic dermatitis <sup>a</sup> 2938(2896)16.0(5.0-25.0)Keloid809(808)N/AConnective tissue diseasesFebrile seizure333(275)N/ADertal diseasesFebrile seizure333(275)N/ADental diseasesFebrile seizure33898(3896)0.1(0.0-1.7)Dental diseasesPeriodontitis3898(3896)0.1(0.0-1.7)Dental diseasesPeriodontitis3898(386)0.1(0.0-1.7)		Peripheral arterial diseases	2683	(2679)	N/A	( , , , , , , , , , , , , , , , , , , ,
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	Liver diseases	Chronic hepatitis B	1346	(1345)	N/A	
Liver cirrhosis2519(2509)N/AUrologic diseasesNephrotic syndrome Urolithiasis1056(1007)N/AMetabolic diseasesOsteoporosis6743(6739)N/AMetabolic diseasesOsteoporosis6743(6739)N/ADiabetes mellitus <sup>b</sup> 39,697(39,686)6.0(2.0–12.0)Dyslipidemia <sup>b</sup> 43,812(43,787)3.0(1.0–7.0)Endocrine diseasesGraves' disease2323(2322)N/AConnective tissue diseasesRheumatoid arthritis4139(4139)7.7(2.6–15.3)Allergic diseasesHay fever5658(5645)N/ADermatologic diseasesDrug eruption585(586)N/AGynecologic diseasesUterine fibroid2938(2896)16.0(5.0–25.0)Keloid809(808)N/A-Gynecologic diseasesFebrile seizure333(275)N/APediatric diseasesGlaucoma4755(4753)3.6(1.1–8.2)Cataract20,002(19,988)1.5(0.2–5.4)Dental diseasesPeriodonitiis3898(3896)0.1(0.0–1.7)OtherAmyotrophic lateral sclerosis <sup>a</sup> 782(771)4.0(2.1–6.9)		Chronic hepatitis C	5819	(5817)	N/A	
Urologic diseases     Nephrotic syndrome     1056 $(1007)$ N/A       Metabolic diseases     Osteoprosis     6307     (6306)     N/A       Metabolic diseases     Osteoprosis     6743     (6739)     N/A       Diabetes mellitus <sup>b</sup> 39,697     (39,686)     6.0     (2.0–12.0)       Dyslipidemia <sup>b</sup> 43,812     (43,787)     3.0     (1.0–7.0)       Endocrine diseases     Graves' disease     2323     (2322)     N/A       Connective tissue diseases     Rheumatoid arthritis     4139     (4139)     7.7     (2.6–15.3)       Allergic diseases     Drug eruption     585     (586)     N/A     50–25.0)       Endocrine diseases     Uterine fibroid     2938     (2896)     16.0     (5.0–25.0)       Keloid     809     (808)     N/A     50–55.0)     N/A     50–55.0)       Gynecologic diseases     Uterine fibroid     5904     (5902)     N/A     50–52.0)       Rediatric diseases     Febrile seizure     333     (275)     N/A     50–52.0)       O		Liver cirrhosis	2519	(2509)	N/A	
Urolithiasis     6307     (6306)     N/A       Metabolic diseases     Osteoporosis     6743     (6739)     N/A       Diabetes mellitus <sup>b</sup> 39,697     (39,686)     6.0     (2.0–12.0)       Dyslipidemia <sup>b</sup> 43,812     (43,787)     3.0     (1.0–7.0)       Endocrine diseases     Graves' disease     2323     (2322)     N/A       Connective tissue diseases     Rheumatoid arthritis     4139     (4139)     7.7     (2.6–15.3)       Allergic diseases     Hay fever     5658     (5645)     N/A     -       Dermatologic diseases     Drug eruption     585     (586)     N/A     -       Keloid     809     (808)     N/A     - </td <td>Urologic diseases</td> <td>Nephrotic syndrome</td> <td>1056</td> <td>(1007)</td> <td>N/A</td> <td></td>	Urologic diseases	Nephrotic syndrome	1056	(1007)	N/A	
Metabolic diseases     Osteoporosis     6743     (6739)     N/A       Diabetes mellitus <sup>b</sup> 39,697     (39,686)     6.0     (2.0–12.0)       Dyslipidemia <sup>b</sup> 43,812     (43,787)     3.0     (1.0–7.0)       Endocrine diseases     Graves' disease     2323     (2322)     N/A       Connective tissue diseases     Rheumatoid arthritis     4139     (4139)     7.7     (2.6–15.3)       Allergic diseases     Hay fever     5658     (5645)     N/A	0	Urolithiasis	6307	(6306)	N/A	
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$ \begin{array}{cccc} Connective tissue diseases & Rheumatoid arthritis & 4139 & (4139) & 7.7 & (2.6-15.3) \\ Allergic diseases & Hay fever & 5658 & (5645) & N/A \\ \hline Dermatologic diseases & Drug eruption & 585 & (586) & N/A \\ Atopic dermatitis^a & 2938 & (2896) & 16.0 & (5.0-25.0) \\ Keloid & 809 & (808) & N/A \\ \hline Gynecologic diseases & Uterine fibroid & 5904 & (5902) & N/A \\ \hline Endometriosis & 1843 & (1843) & N/A \\ \hline Pediatric diseases & Febrile seizure & 333 & (275) & N/A \\ \hline Ophthalmologic diseases & Glaucoma & 4755 & (4753) & 3.6 & (1.1-8.2) \\ \hline Catract & 20,002 & (19,988) & 1.5 & (0.2-5.4) \\ \hline Dental diseases & Periodonitiis & 3898 & (3896) & 0.1 & (0.0-1.7) \\ \hline Other & Amyotrophic lateral sclerosis^a & 782 & (771) & 4.0 & (2.1-6.9) \\ \hline \end{array}$	Endocrine diseases	Graves' disease	2323	(2322)	N/A	. ,
Allergic diseases     Hay fever     5658     (5645)     N/A       Dermatologic diseases     Drug eruption     585     (586)     N/A       Atopic dermatitis <sup>a</sup> 2938     (2896)     16.0     (5.0–25.0)       Keloid     809     (808)     N/A       Gynecologic diseases     Uterine fibroid     5904     (5902)     N/A       Pediatric diseases     Uterine fibroid     1843     (1843)     N/A       Ophthalmologic diseases     Febrile seizure     333     (275)     N/A       Ophthalmologic diseases     Glaucoma     4755     (4753)     3.6     (1.1–8.2)       Dental diseases     Periodontitis     3898     (3896)     0.1     (0.0–1.7)       Other     Amyotrophic lateral sclerosis <sup>a</sup> 782     (771)     4.0     (2.1–6.9)	Connective tissue diseases	Rheumatoid arthritis	4139	(4139)	7.7	(2.6 - 15.3)
Dermatologic diseases     Drug eruption     585     (586)     N/A       Atopic dermatitis <sup>a</sup> 2938     (2896)     16.0     (5.0–25.0)       Keloid     809     (808)     N/A       Gynecologic diseases     Uterine fibroid     5904     (5902)     N/A       Pediatric diseases     Uterine fibroid     333     (275)     N/A       Ophthalmologic diseases     Glaucoma     4755     (4753)     3.6     (1.1–8.2)       Dental diseases     Periodontitis     3898     (3896)     0.1     (0.0–1.7)       Other     Amyorophic lateral sclerosis <sup>a</sup> 782     (771)     4.0     (2.1–6.9)	Allergic diseases	Hay fever	5658	(5645)	N/A	. ,
Atopic dermatitis <sup>a</sup> 2938     (2896)     16.0     (5.0–25.0)       Keloid     809     (808)     N/A       Gynecologic diseases     Uterine fibroid     5904     (5902)     N/A       Endometriosis     1843     (1843)     N/A       Pediatric diseases     Febrile seizure     333     (275)     N/A       Ophthalmologic diseases     Glaucoma     4755     (4753)     3.6     (1.1–8.2)       Cataract     20,002     (19,988)     1.5     (0.2–5.4)       Dental diseases     Periodontitis     3898     (3896)     0.1     (0.0–1.7)       Other     Amyotrophic lateral sclerosis <sup>a</sup> 782     (771)     4.0     (2.1–6.9)	Dermatologic diseases	Drug eruption	585	(586)	N/A	
Keloid     809     (808)     N/A       Gynecologic diseases     Uterine fibroid     5904     (5902)     N/A       Endometriosis     1843     (1843)     N/A       Pediatric diseases     Febrile seizure     333     (275)     N/A       Ophthalmologic diseases     Glaucoma     4755     (4753)     3.6     (1.1-8.2)       Cataract     20,002     (19,988)     1.5     (0.2-5.4)       Dental diseases     Periodonitiis     3898     (3896)     0.1     (0.0-1.7)       Other     Amyotrophic lateral sclerosis <sup>a</sup> 782     (771)     4.0     (2.1-6.9)	C	Atopic dermatitis <sup>a</sup>	2938	(2896)	16.0	(5.0 - 25.0)
Gynecologic diseases     Uterine fibroid     5904     (5902)     N/A       Endometriosis     1843     (1843)     N/A       Pediatric diseases     Febrile seizure     333     (275)     N/A       Ophthalmologic diseases     Glaucoma     4755     (4753)     3.6     (1.1-8.2)       Cataract     20,002     (19,988)     1.5     (0.0-5.4)       Dental diseases     Periodonitis     3898     (3896)     0.1     (0.0-1.7)       Other     Amyotrophic lateral sclerosis <sup>a</sup> 782     (771)     4.0     (2.1-6.9)		Keloid	809	(808)	N/A	(,
Endometriosis     1843     (1843)     N/A       Pediatric diseases     Febrile seizure     333     (275)     N/A       Ophthalmologic diseases     Glaucoma     4755     (4753)     3.6     (1.1-8.2)       Cataract     20,002     (19,988)     1.5     (0.2-5.4)       Dental diseases     Periodonitiis     3898     (3896)     0.1     (0.0-1.7)       Other     Amyotrophic lateral sclerosis <sup>a</sup> 782     (771)     4.0     (2.1-6.9)	Gynecologic diseases	Uterine fibroid	5904	(5902)	N/A	
Pediatric diseases     Febrile seizure     333     (275)     N/A       Ophthalmologic diseases     Glaucoma     4755     (4753)     3.6     (1.1–8.2)       Cataract     20,002     (19,988)     1.5     (0.2–5.4)       Dental diseases     Periodontitis     3898     (3896)     0.1     (0.0–1.7)       Other     Amyotrophic lateral sclerosis <sup>a</sup> 782     (771)     4.0     (2.1–6.9)	, , , , , , , , , , , , , , , , , , ,	Endometriosis	1843	(1843)	N/A	
Ophthalmologic diseases     Glaucoma     4755     (4753)     3.6     (1.1–8.2)       Cataract     20,002     (19,988)     1.5     (0.2–5.4)       Dental diseases     Periodontitis     3898     (3896)     0.1     (0.0–1.7)       Other     Amyotrophic lateral sclerosis <sup>a</sup> 782     (771)     4.0     (2.1–6.9)	Pediatric diseases	Febrile seizure	333	(275)	N/A	
Cataract     20,002     (19,988)     1.5     (0.2–5.4)       Dental diseases     Periodontitis     3898     (3896)     0.1     (0.0–1.7)       Other     Amyotrophic lateral sclerosis <sup>a</sup> 782     (771)     4.0     (2.1–6.9)	Ophthalmologic diseases	Glaucoma	4755	(4753)	3.6	(1.1 - 8.2)
Dental diseases     Periodontitis     3898     (3896)     0.1     (0.0-1.7)       Other     Amyotrophic lateral sclerosis <sup>a</sup> 782     (771)     4.0     (2.1-6.9)		Cataract	20,002	(19,988)	1.5	(0.2 - 5.4)
Other Amyotrophic lateral sclerosis <sup>a</sup> 782 (771) 4.0 (2.1–6.9)	Dental diseases	Periodontitis	3898	(3896)	0.1	(0.0 - 1.7)
	Other	Amyotrophic lateral sclerosis <sup>a</sup>	782	(771)	4.0	(2.1 - 6.9)

Abbreviation: N/A, not available.

<sup>a</sup> The duration of disease was calculated based on the time of disease onset to the time of entry into the registry.

<sup>b</sup> Because we surveyed calendar year of diagnosis for these diseases, the periods from diagnosis were not measured in units of days and months.

#### Biobanking of biological samples and clinical information

about the distribution of the samples is available at the project website (https://biobankjp.org/index.html; Japanese only).<sup>8</sup>

The study flow related to the collection of biological samples and clinical information is shown in Fig. 2. For biological samples, we collected DNA and serum samples from participants at the cooperating hospitals and stored them at the BBJ DNA bank and serum bank, respectively. Details of the blood sampling and storage processes are described in the Blood Sampling and Storage section. Clinical information was initially stored in the local server at the cooperating hospitals and was subsequently sent to the BBJ at the end of every year after anonymization.

Samples stored in the BBJ were provided to research institutions and companies beginning in 2005 after receiving approval from the Sample Providing Committee of this project. Detailed information Baseline survey

We collected baseline clinical information through interviews and reviews of medical records using a standardized questionnaire (Table 1); full details of the questionnaire are available at the project website (https://biobankjp.org/sample/pdf/list7.1.4.pdf; Japanese only). The common items addressed during each interview included smoking and alcohol habits, height, weight, systolic and diastolic blood pressure, past history and family history of various diseases, frequency of food intake and physical exercise, and reproductive history (for female participants). The common



Fig. 2. The flow of the collection of the sample.

items collected from medical record reviews included information about birth year, sex, drug use within one month before study entry, history of adverse drug events, and routine laboratory examination data (including complete blood count, urinalysis, and biochemical tests such as measurements of liver enzymes, kidney function, lipids, and blood sugar).

Disease-specific laboratory tests and imaging data were collected for 15 disease groups. For example, we collected information related to surgical history, chemotherapy, hormonal therapy, radiotherapy, and tumor markers for 13 types of cancers. Echocardiogram and coronary angiography information were collected for cardiovascular diseases. Detailed clinical information for each case, such as disease onset, symptoms, subtypes, severity, and complications, was collected separately for disease-specific items. Because the BBJ included both incident and prevalent cases, the duration of disease at registration was calculated based on the date of onset or diagnosis of disease and the date of enrollment. All surveys were performed by medical coordinators at cooperating hospitals.

In this analysis, body mass index  $(kg/m^2)$  was calculated on the basis of the self-reported height and body weight. Hypertension was defined as a systolic blood pressure  $\geq$ 140 mmHg, a diastolic blood pressure  $\geq$ 90 mmHg, or a prescription of antihypertensive drugs.

# Data cleansing

To improve the quality of the baseline survey data, we reviewed all data items and performed data cleansing for 4627 out of 17,850 items that were available for >50% of participants or that were determined to be clinically important variables (e.g., TNM classification for cancer). We checked the distribution of all numeric data and excluded outliers for each variable. For categorical data, we checked the concordance of related variables and excluded discordant data in order to achieve consistency among the values.

## Blood sampling and storage

A 14 mL sample of whole blood was obtained from each participant at baseline using two 7 mL EDTA-containing tubes. One

7 mL sample of whole blood was sent to one of three commercial laboratories (SRL, BML, and MBC, Japan) for DNA extraction. After DNA was extracted according to the standard procedures in each laboratory, DNA concentration was adjusted to 100 ng/ $\mu$ L and dispensed into three 1 mL tubes with 2D barcodes at the bottom. All DNA tubes were stored at 4–10 °C and delivered to the BBJ. After checking the concordance of the 2D barcodes on the DNA tubes with participant anonymized numbers, all DNA samples were stored in the DNA bank at 4 °C (Fig. 3). For children or participants with whom there were difficulties in drawing blood, we collected buccal swabs, nail trimmings, or hair trimmings to extract DNA.

Another 7 mL sample of whole blood was centrifuged according to standard procedures at each cooperating hospital, and the resultant serum was dispensed into three 1 mL tubes and labeled with 2D barcodes. All serum samples were initially stored at -80 °C at cooperating hospitals. After several samples were stored, these samples were then delivered to the BBJ. After checking the concordance of the 2D barcodes on the serum tubes with participant anonymized numbers, all serum samples were stored in the



Fig. 3. Picture of DNA bank (automated DNA storage system).



Fig. 4. Picture of serum bank.

serum bank at -150 °C (Fig. 4). Participants were requested to provide serum samples once a year starting the year following enrollment until March 2013.

### Follow-up surveys

After the baseline survey, we continuously collected clinical information from participants through reviews of medical records

once a year until March 2013. If a participant developed a new disease from among the 47 target diseases, medical coordinators registered this new disease and collected relevant clinical information from medical records.

In addition, we collected survival data for participants with any of 32 of the 47 target diseases based on the participants' registered disease in the 2010 medical record survey. Medical coordinators initially checked the date of last visit and identified participants who had not visited the hospital in more than one year or who had died during the follow-up period. Hospitals requested a copy of the resident card for these participants from local government offices. Medical coordinators then recorded whether the participants were alive, had moved, were unidentified, or had died. For participants who had moved, new addresses were recorded for the next survival survey. For deceased participants, medical coordinators recorded the date of death. We obtained vital statistics from the Statistics and Information Department of the Ministry of Health, Labour and Welfare in Japan and identified the cause of death according to ICD-10 code by matching birth date, date of death, sex, and local government code.

## Ethical review

The study protocol for the BBJ Project was approved by the research ethics committees at the Institute of Medical Science, the University of Tokyo, the RIKEN Yokohama Institute, and the 12 cooperating hospitals. All participants gave written consent to participate in the study.



Fig. 5. Flow diagram for baseline and follow-up survey data of study participants.

# Results

A flow diagram describing the process for the baseline survey and survival survey is shown in Fig. 5. There were 200,000 patients who were enrolled in the study. Since the clinical information of participants who withdrew informed consent or who were mistakenly enrolled was already removed from the clinical database, baseline data for 199,982 participants were available in this analysis.

Of the 200,000 participants, 161,823 participants were registered with any of 32 diseases during the 2010 medical record survey. Among them, we excluded 20,211 participants who were enrolled at hospitals that withdrew from the BioBank Project, those who refused to complete the follow-up survey, those who withdrew informed consent, or those who were mistakenly enrolled. Finally, survival data for 141,612 participants were available for analysis. The follow-up rate was 97.0%, and the mean follow-up period was 7.7 years. The details of the results of the follow-up survey are described in another report.<sup>9</sup>

The total number of cases was 291,274 at baseline (Table 2). The largest number of cases was related to dyslipidemia followed by diabetes mellitus. Information on disease onset or diagnosis was collected for 31 diseases. When we evaluated disease duration at registration, the median disease duration was short for most cancer cases, but was long for cases of atopic dermatitis, bronchial asthma, and rheumatoid arthritis, indicating that the proportion of prevalent cases was high for these diseases. Among the participants, 53.1% were male (Table 3). The average age was 62.7 years for male patients and 61.5 years for female patients. Among participants aged 20 years or older, 27.5% of male and 23.7% of female patients were overweight or obese. The proportion of current smokers was 27.3% for male patients and 10.3% for female patients; the proportion of current drinkers was 54.9% for male patients and 23.6% for female patients. About 51% of male patients and 43% of female patients were defined as having hypertension. Full details regarding baseline characteristics are described in another report.<sup>10</sup>

#### Discussion

The BBJ Project enrolled approximately 200,000 participants during the first 5-year period of the study. DNA and serum samples stored in the BBJ have enabled investigation of novel genetic factors and new biomarkers related to common diseases. The collected clinical information and follow-up survey data have provided knowledge about the general clinical features of many common diseases in Japan, including both therapeutic conditions and the course of the diseases. Further analyses of the genomic data, clinical information, and follow-up surveys will provide important information regarding the interaction of genetic and clinical factors, and ideally, will eventually contribute to optimized medical treatment that takes into account the individual genetic makeup of the patient.

In recent years, many large-scale biobanks have been established in Europe<sup>11</sup> and the United States,<sup>12</sup> including the UK Biobank,<sup>13</sup> the Auria Biobank,<sup>14</sup> the Estonian Biobank,<sup>15</sup> the Kaiser Biobank,<sup>12</sup> the Million Veteran Program,<sup>16</sup> and the Precision Medicine Initiative Cohort.<sup>17</sup> The UK Biobank has already collected samples from 500,000 participants in the United Kingdom.<sup>13</sup> The Precision Medicine Initiative Cohort plans to collect samples from 1 million participants in the United States.<sup>17</sup> In Japan, the Tohoku Medical Megabank is collecting biological specimens from 150,000 residents.<sup>18</sup> However, most of these biobanks are population-based. Large, patient-based biobanks, such as the BioVU<sup>19</sup> and Mayo Clinic Biobank,<sup>20</sup> are limited. To our knowledge, the BBJ is the first patient-based biobank in the world. This is an advantage in

Tabl	e :

Characteristics of study participants in the BioBank Japan Study.

	Male		Female	Female	
	N	%	N	%	
Sex	106,093	53.1	93,696	46.9	
Age group at entry (years)					
<20	1413	1.3	982	1.0	
20-29	2062	1.9	2842	3.0	
30-39	4815	4.5	6534	7.0	
40-49	8302	7.8	9483	10.1	
50-59	19,515	18.4	16,410	17.5	
60-69	31,637	29.8	23,796	25.4	
70–79	30,065	28.3	24,106	25.7	
≥80	8272	7.8	9522	10.2	
Unknown	12	0.0	21	0.0	
BMI <sup>a</sup> (kg/m <sup>2</sup> )					
Lean (BMI < 18.5)	5653	5.4	8525	9.2	
Normal (18.5 $\leq$ BMI < 25)	63,137	60.3	55,330	59.7	
Overweight ( $25 \le BMI < 30$ )	24,865	23.8	17,826	19.2	
Obese ( $30 \le BMI$ )	3898	3.7	4202	4.5	
Unknown	7115	6.8	6810	7.3	
Smoking status <sup>a</sup>					
Never smoker	25,690	24.5	71,637	77.3	
Ex-smoker	44,919	42.9	8521	9.2	
Current smoker	28,524	27.3	9505	10.3	
Smoker, unknown current status	3547	3.4	1293	1.4	
Unknown if ever smoked	1988	1.9	1737	1.9	
Alcohol intake <sup>a</sup>					
Never drinker	30,933	29.6	64,987	70.1	
Ex-drinker	13,618	13.0	3614	3.9	
Current drinker (0–10 g/day)	14,610	14.0	11,818	12.7	
Current drinker (10–20 g/day)	10,296	9.8	3801	4.1	
Current drinker (20–60 g/day)	20,884	20.0	3251	3.5	
Current drinker ( $60 + g/day$ )	7496	7.2	765	0.8	
Drinker, unknown current status	4175	4.0	2277	2.5	
Unknown	2656	2.5	2180	2.4	
Hypertension					
Normotension	37,898	35.7	40,692	43.4	
Hypertension	53,962	50.9	38,127	40.7	
Unknown	14,233	13.4	14,877	15.9	
Physical exercise					
Three or more times a week	21,558	20.3	20,159	21.5	
Once or twice a week	3692	3.5	6132	6.5	
No habit	68,367	64.4	56,796	60.6	
Unknown	12,476	11.8	10,609	11.3	

Because the sex was unknown, 193 participants were excluded from this analysis. Abbreviation: BML body mass index.

<sup>a</sup> People of unknown age or under the age of 20 were excluded.

analyzing risk factors of disease prognosis because the BBJ enables examination of data with the longest follow-up period available.

Patient-based biobanks allow for the identification of susceptibility genes for common diseases because large numbers of cases are registered. In contrast, population-based biobanks allow for estimation of environmental exposures and gene—environment interactions, but long-term follow-up is needed because a large number of disease onset cases is needed to achieve sufficient statistical power.<sup>21</sup> Therefore, patient-based biobanks and populationbased biobanks should work in cooperation with the goal of implementing personalized, precision medicine in the future.

#### **Conflicts of interest**

The authors declare they have no conflict of interest with respect to this research study and paper.

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## Appendix A

### Author list for the BioBank Japan Cooperative Hospital Group.

Members of medical institutions cooperating on the BioBank Japan Project who coauthored this paper include Masaki Shiono, Kazuo Misumi, Reiji Kaieda and Hiromasa Harada (Tokushukai Hospitals): Shiro Minami, Mitsuru Emi and Naova Emoto (Nippon Medical School); Hiroyuki Daida, Katsumi Miyauchi and Akira Murakami (Juntendo University); Satoshi Asai, Mitsuhiko Moriyama and Yasuo Takahashi (Nihon University); Tomoaki Fujioka and Wataru Obara (Iwate Medical University); Seijiro Mori and Hideki Ito (Tokyo Metropolitan Institute of Gerontology); Satoshi Nagayama and Yoshio Miki (The Cancer Institute Hospital of JFCR); Akihide Masumoto and Akira Yamada (Aso Iizuka Hospital); Yasuko Nishizawa and Ken Kodama (Osaka Medical Center for Cancer and Cardiovascular Diseases); Hiromu Kutsumi and Yoshihisa Sugimoto (Shiga University of Medical Science); Yukihiro Koretsune and Hideo Kusuoka (National Hospital Organization, Osaka National Hospital); and Hideki Yanai (Fukujuji Hospital).

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