The value of **Innovative Medicine** in Japan

PhRMA
RESEARCH • PROGRESS • HOPE

APRIL 12, 2013

Executive summary

Japan's healthcare is one of the best in the world, however risks exist that can undermine this world-class care system

- World-class healthcare system
  - **Highest** life expectancy, and one of the **lowest mortality rates**
  - Easy physician **access** with low healthcare spending compared to other countries
- However, risks exist that could undermine this system
  - Rapidly **ageing population** and the need to care for the elderlies
  - Widening **funding gap** due to rising healthcare cost and higher fiscal constraint

Investments in healthcare, particularly in innovative medicine can help mitigate these risks and create significant social and financial benefits

- Thanks to favorable government policies, a total of **176** medicines have been introduced in the past five years. These medicines have substantially improved people's quality of life
- These medicines generated significant financial and economic benefit:
  - more **efficient use of medical resources** and save cost
  - enable workers to be more **productive** thanks to less **absenteeism** and **disability**. Increase quality lifespan so people work longer
- Using available Japanese data, a study of five best-in-class drugs demonstrated value of **1,300 – 1,500 bn JPY**, representing **16%** of the total medical spending in these disease areas

Japanese government should continue to promote innovation through policies and investment in healthcare

- Benefits all stakeholders – e.g. patients, physicians and government etc.
- Japanese government should continue to promote innovation through policies and additional funding

Executive summary

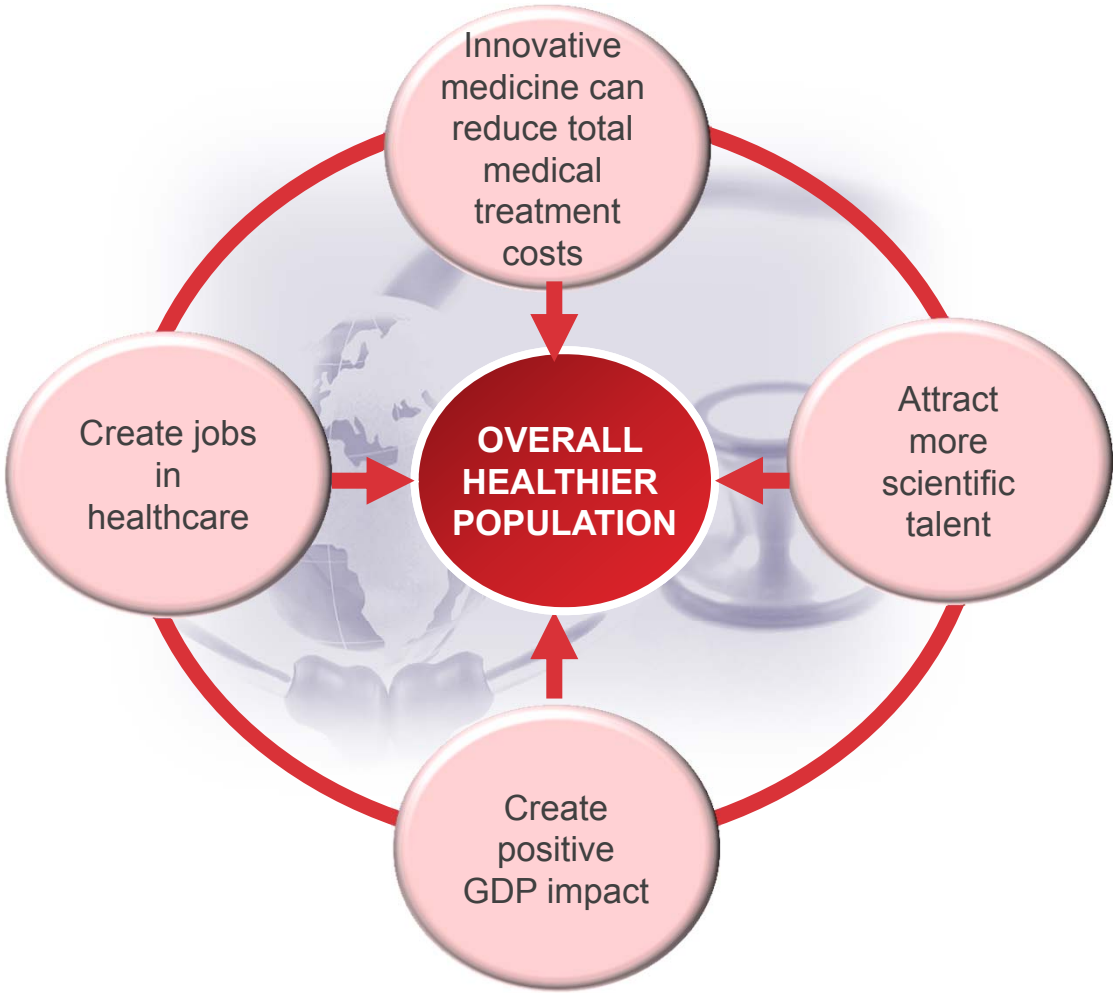
Japan has a world class healthcare system:

- Easy access
- One of the best outcomes
- Spending level relatively low

There are risks that can undermine the healthcare system

- Ageing population
- Widening funding gap

Investments in healthcare can generate significant value:



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Japan’s healthcare is the one of the best in the world, however risks exist that can undermine this system

Investments in healthcare, particularly in innovative medicine can help mitigate these risks

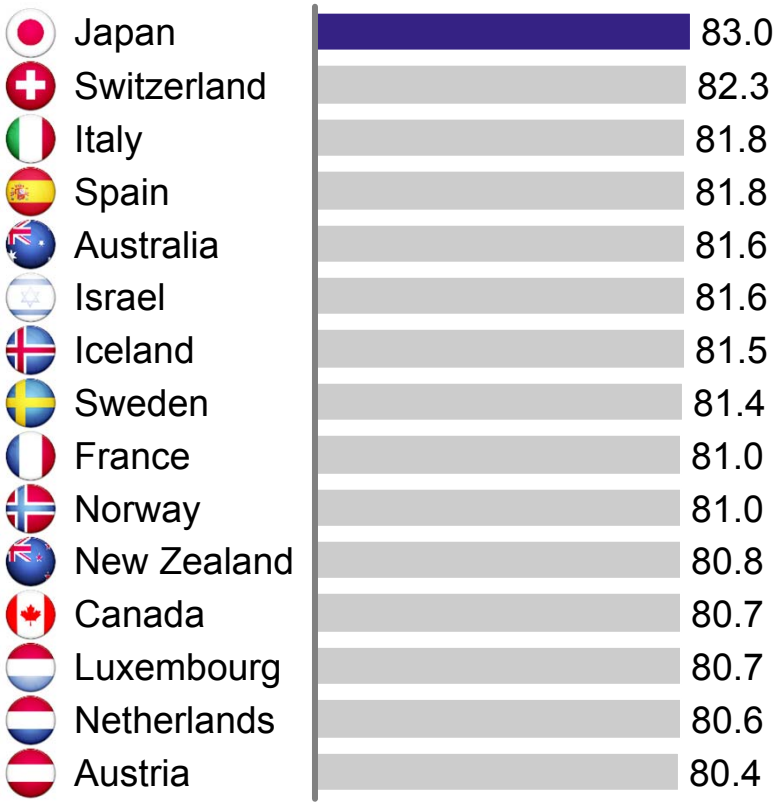
The importance of innovative medicine has implications on a number of stakeholders

Japan has one of the healthiest populations in the world – Highest life expectancy and one of the lowest infant mortality rate

RANKED FROM BEST TO WORST

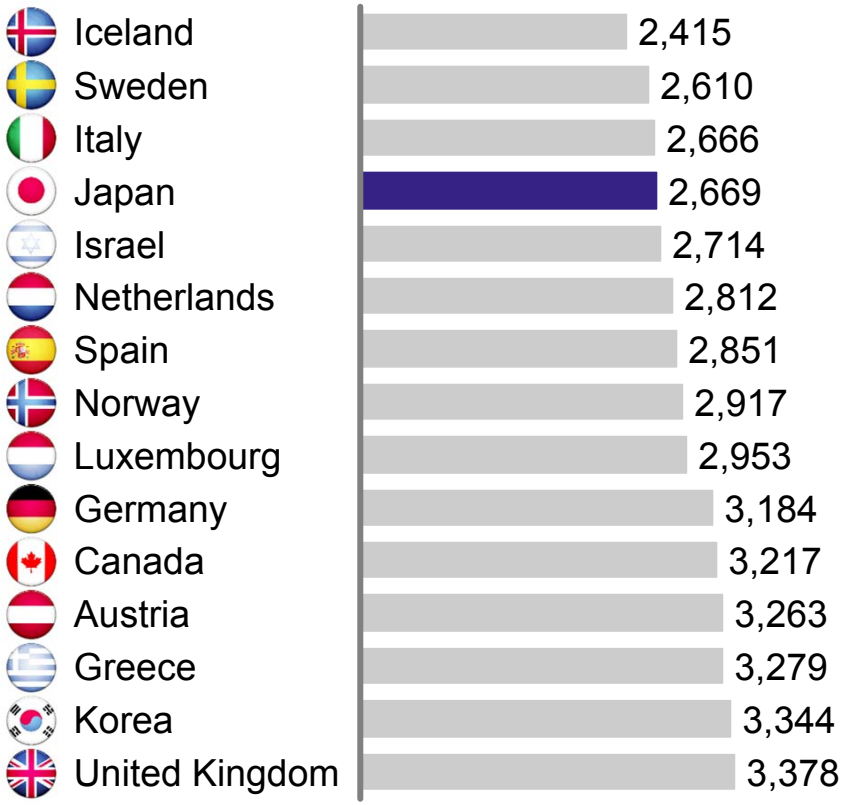
Life expectancy at birth

Years; 2009



Potential years of life lost[1]

Years lost/100,000 population aged 0-69; 2009



1 Potential years of life lost (PYLL) is a summary measure of premature mortality which provides an explicit way of weighting deaths occurring at younger ages, which are, a priori, preventable

SOURCE: OECD

Japan also has the lowest mortality from major disease (e.g., cancer, circulatory diseases, diabetes)

RESULTS OF INTERNATIONAL COMPARISON OF HEALTH INDICATORS

Overall rating

1	Japan	A
2	Switzerland	A
3	Italy	A
4	Norway	B
5	Finland	B
6	Sweden	B
7	France	B
8	Australia	B
9	Germany	B
10	Canada	B
11	Netherlands	C
12	Belgium	C
13	Austria	C
14	UK	C
15	Ireland	D
16	Denmark	D
17	US	D

Mortality rate for seven diseases in Japan

Indicators	Rating[1]
Mortality Due to Cancer	A
Mortality Due to Circulatory Diseases	A
Mortality Due to Respiratory Diseases	C
Mortality Due to Diabetes	A
Mortality Due to Musculoskeletal System Diseases	A
Mortality Due to Mental Disorders	A
Mortality Due to Medical Misadventures	A

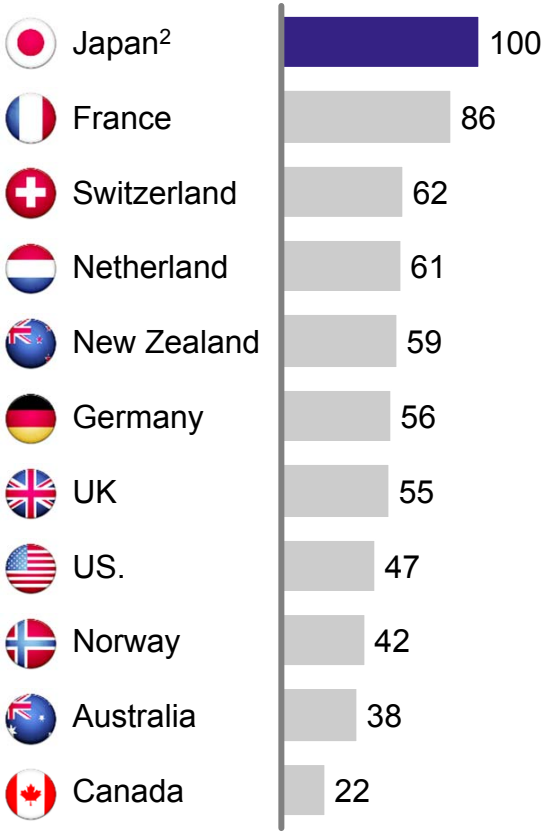
1 A country receives a report card rating of “A” on a given indicator if its score is in the top quartile; a “B” if its score is in the second quartile; a “C” if its score is in the third quartile; and a “D” if its score is in the bottom quartile

SOURCE: Conference Board of Canada based on OECD Health Data 2009

Japanese patients enjoy the best physician access and care quality

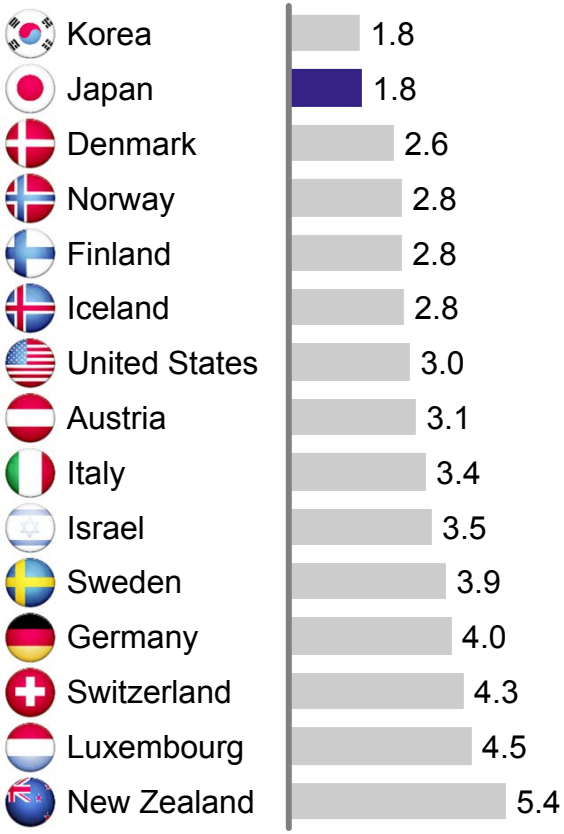
Good access

Almost all (>80%) patients can get same/next-day appointment[1]
%; 2012



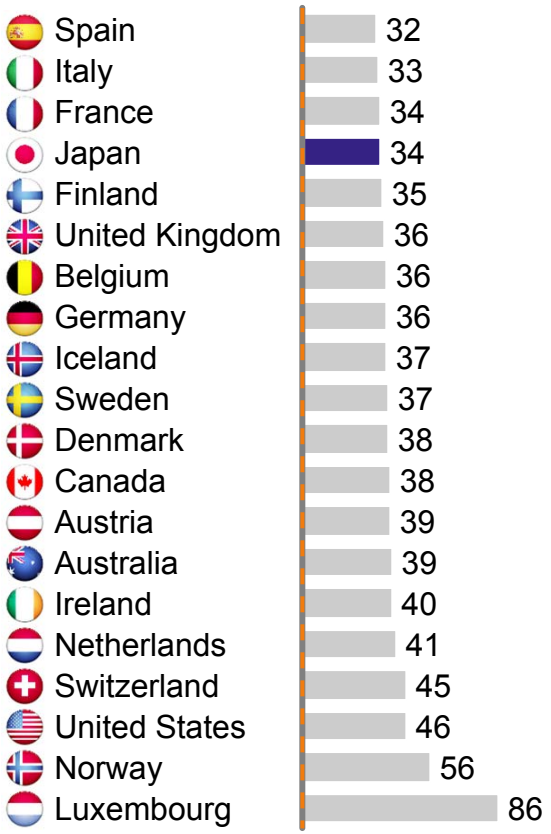
Good quality

In-hospital case-fatality rates within 30 days after admission for ischemic stroke, %; 2009



Moderate cost

Health-care cost per capita[2]
$ thousand PPP; 2009

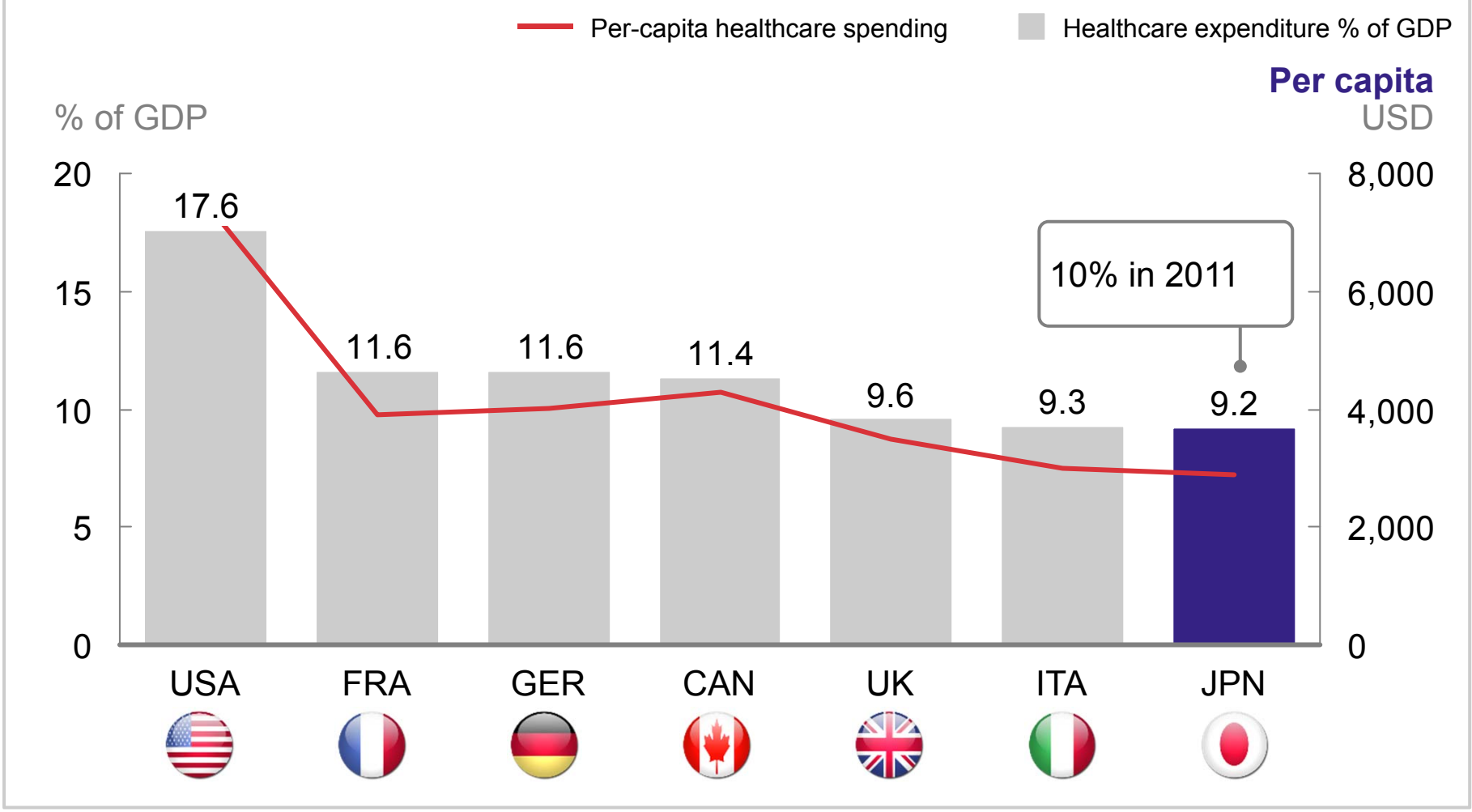


1 Percent of physician reporting that Almost all (>80%) of patients can get same/next-day appointment when sick
2 Data on Japan is from expert insights and MHLW data.
3 The data for Japan, Portugal, and Australia for 2008.

SOURCE: OECD Health Data; Commonwealth Fund International Survey; MHLW

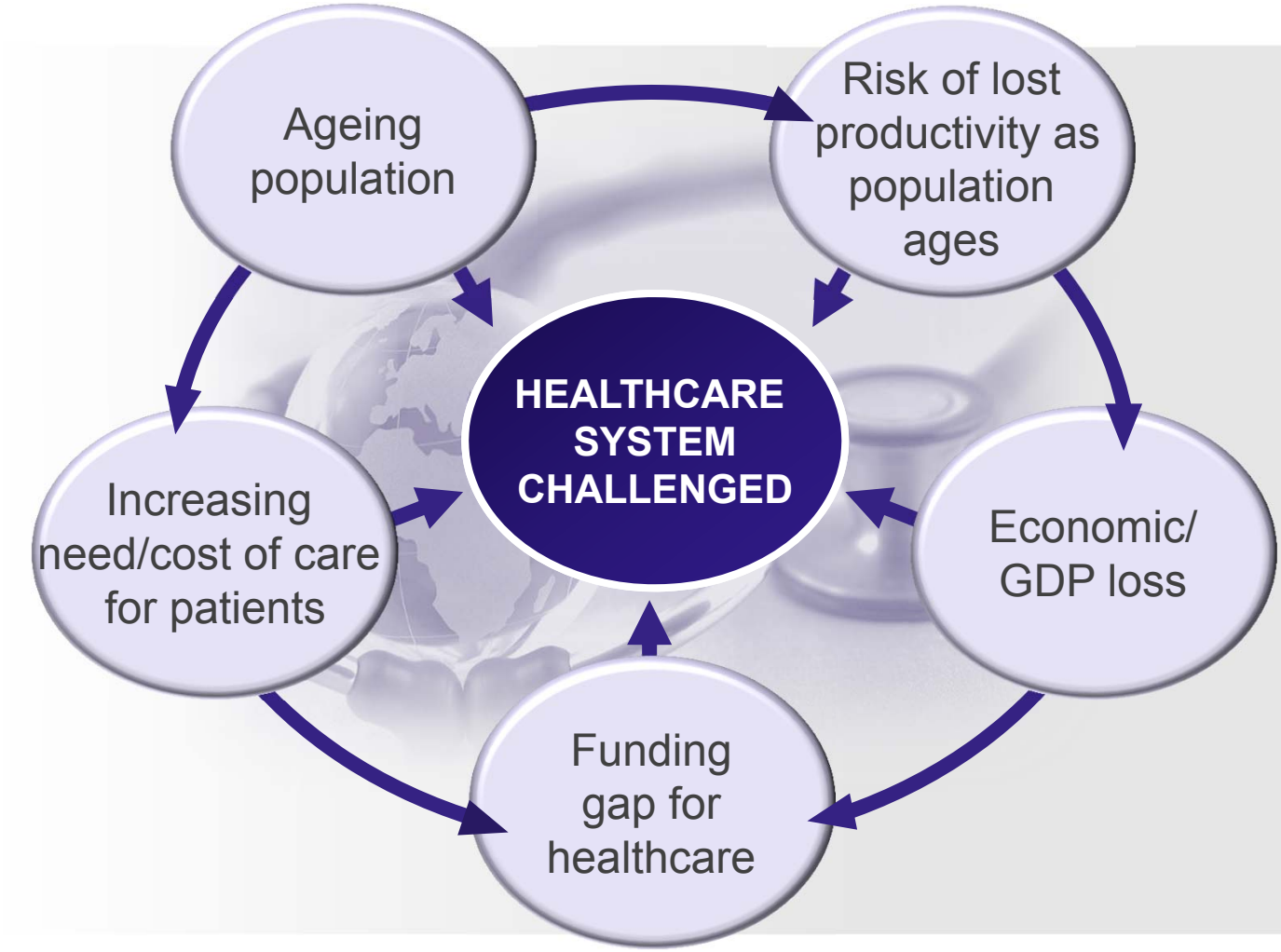
Japan also has the lowest total healthcare spending as a percentage of GDP, and per capita spending among G7 counties

National healthcare spending as Per-cent of GDP and Per-capita spending[1] (2010)



SOURCE: OECD;MHL;World bank

However, emerging demographic and economic risks could undermine this world-class healthcare system



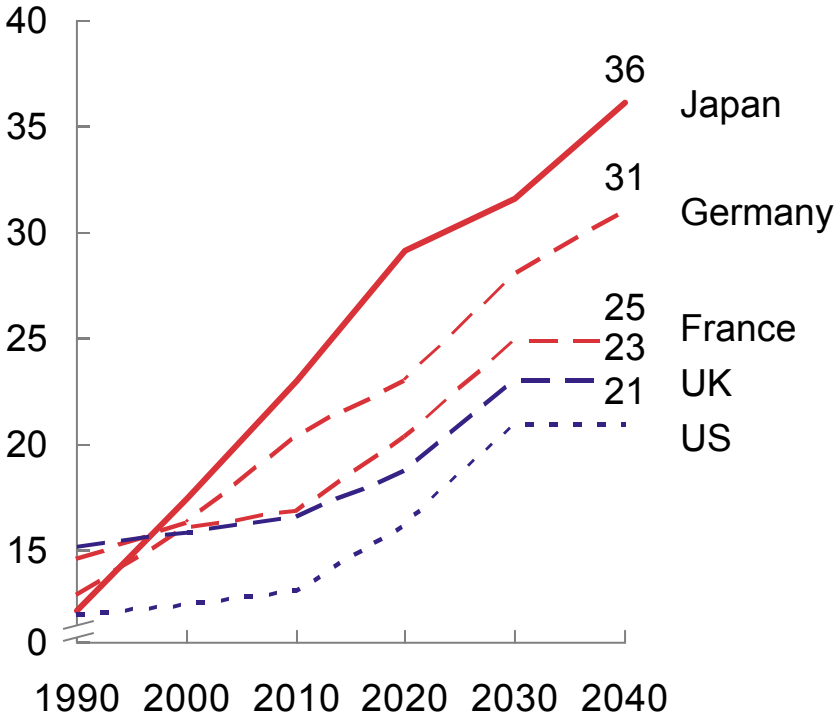
Challenged healthcare system can

- Impact population's quality life
- Affect social stability

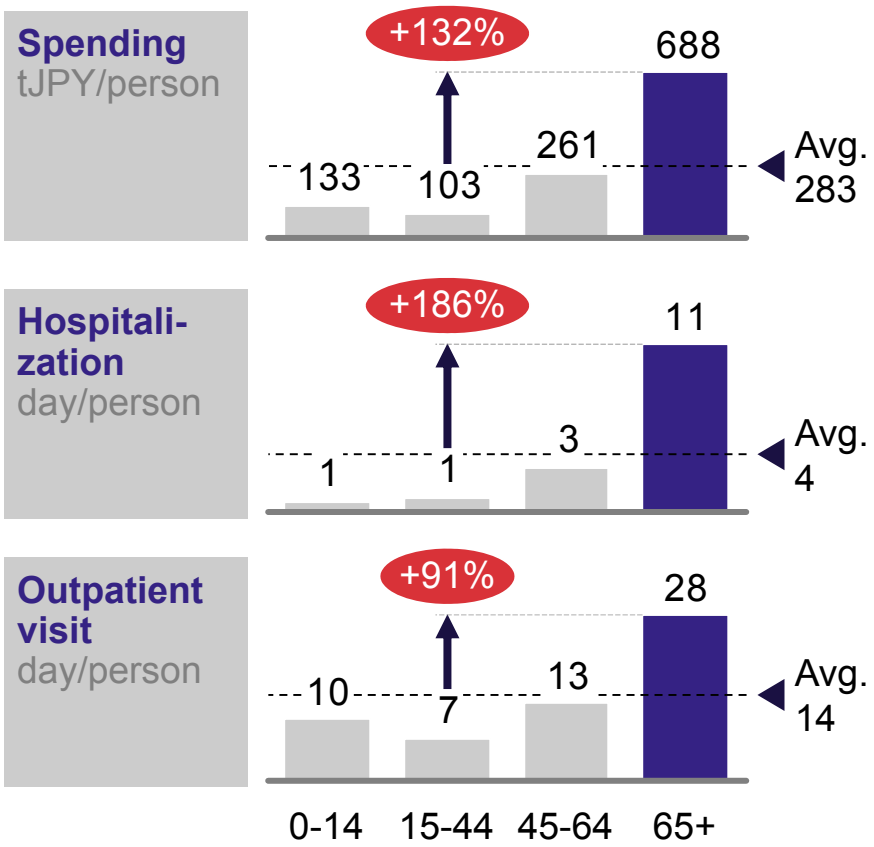
Ageing population and the need/cost to provide care for the elderlies

Japanese population is ageing rapidly to unprecedented level

Population age 65 and over
% of population



Elderly uses healthcare more than average population, 2008

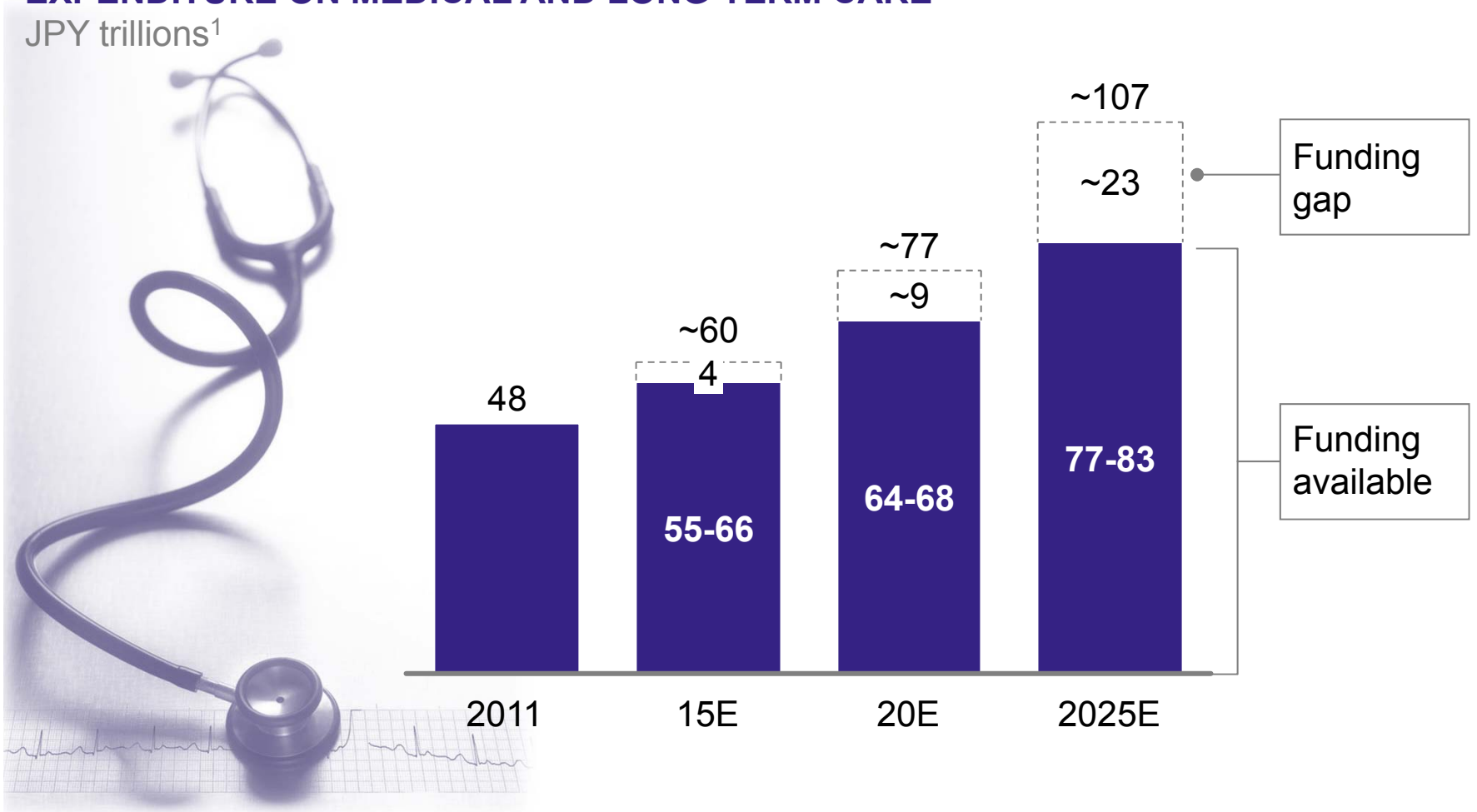


SOURCE: UN; MHLW

Widening funding gap for healthcare expenditures

EXPENDITURE ON MEDICAL AND LONG-TERM CARE

JPY trillions[1]



1 Based on 2008 estimate at Prime Minister Office (“社会保障国民会議”)
2 Based on 2011 estimate at Prime Minister Office (“社会保障・税との一体改革集中検討会議”)

SOURCE: MHLW, Cabinet Secretariat

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Japan’s healthcare is the one of the best in the world, however risks exist that can undermine this system

Investments in healthcare, particularly in innovative medicine can mitigate these risks

The importance of innovative medicine has implications on a number of stakeholders

Investments in healthcare helps mitigate these risks and maintain Japan's healthcare standards at high levels

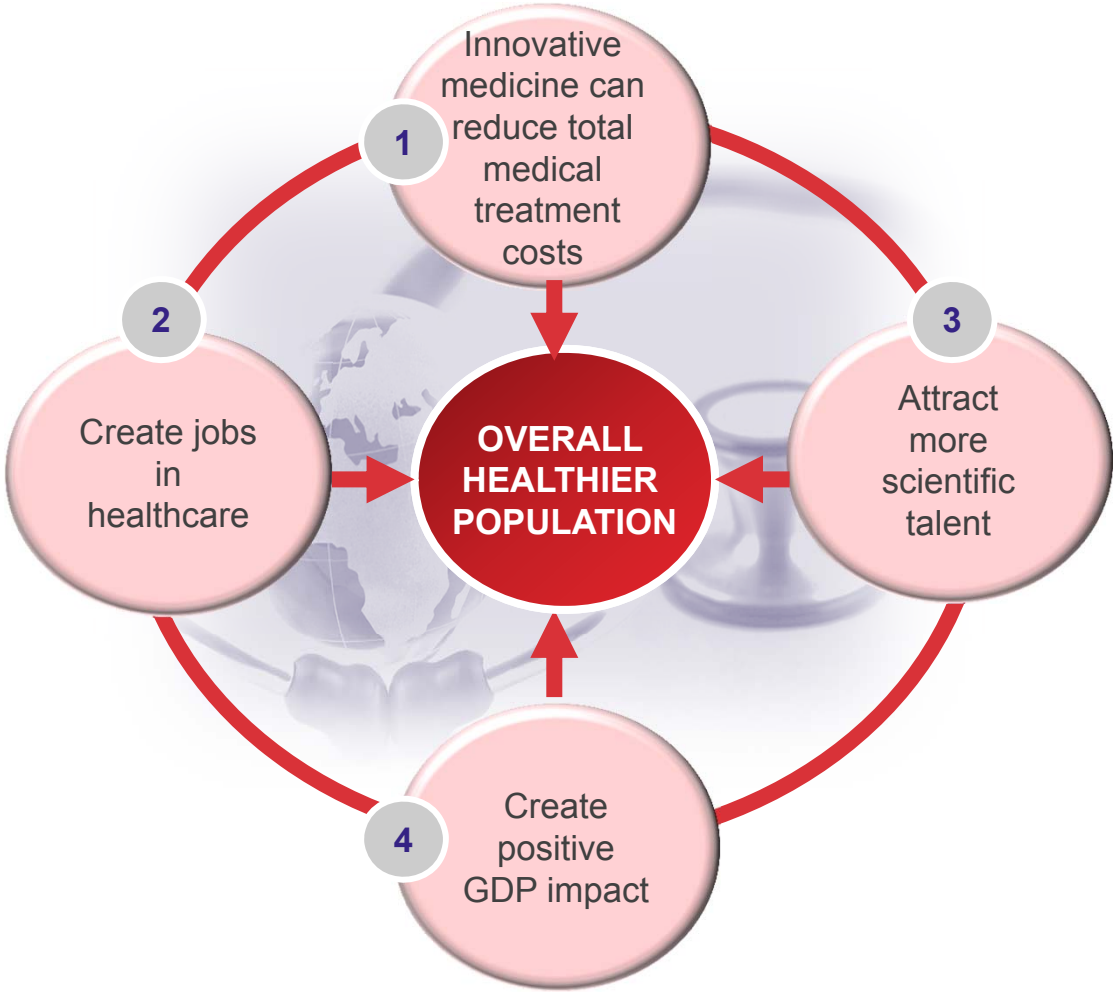
Japan has a world class healthcare system:

- Easy access
- One of the best outcomes
- Spending level relatively low

There are risks that can undermine the healthcare system

- Ageing population
- Widening funding gap

Investments in healthcare can generate significant value:



1 Innovative medicine is the most realistic and impactful driver to enhance healthcare outcomes, loosening fiscal constraints

Reduce the life-time cost of treatments

- Innovative medicine can more effectively treat or prevent diseases
  - Leading to less need for care or hospitalization, particularly for elderlies

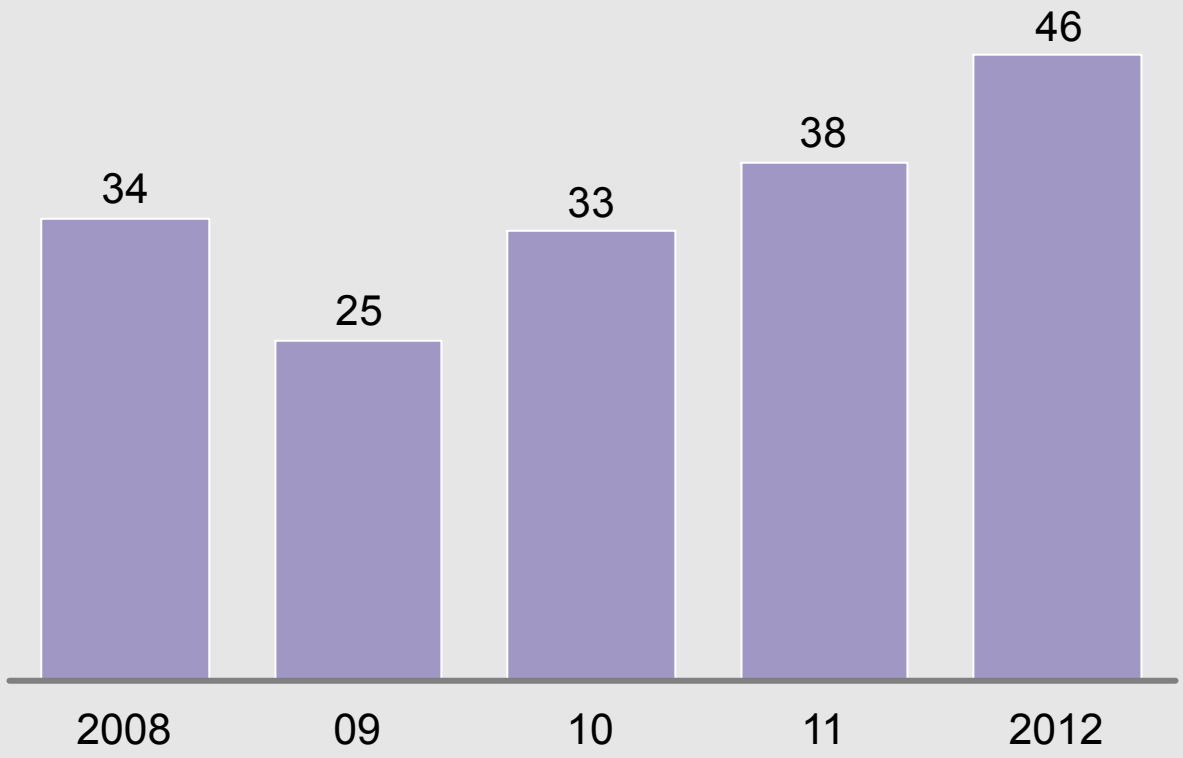
Avoid productivity loss

- Improve patients' health level to above productivity level
- Thus contribute to additional GDP growth to reduce funding gap

Innovative medicine introductions in Japan have been speeding up, thanks to favorable government policy

New medicine introductions, 2008-12

Molecule count



- **A total of 176 medicines have been introduced in the past five years**
- **Average new medicine review time has been reduced from 22 months to 11 months**
- **Simultaneous global trials have been increasing**

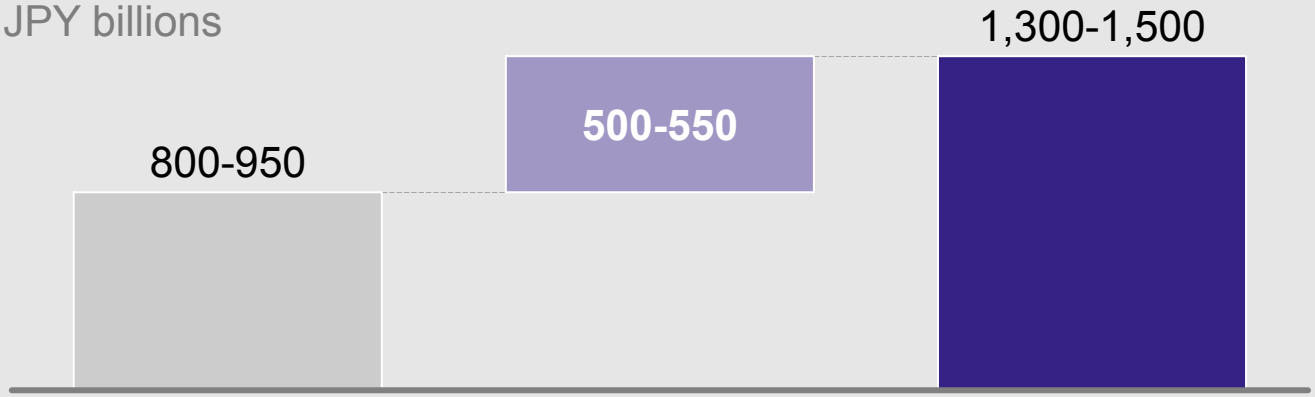
Source: MHLW; PMDA; Asu no Shinyaku

We selected five best-in-class medicines where Japanese data are available and quantified their financial and economic benefits

5 disease areas
Diabetes
Chronic obstructive pulmonary disease
Chronic kidney disease
Stroke prevention atrial fibrillation
Depression

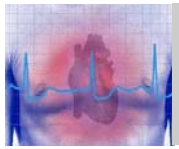
TOTAL VALUE OF 5 MEDICINES

JPY billions



- Allows more efficient use of medical resources, and saves cost through better effectiveness and fewer side effects
- Enables workers to be more productive thanks to less absenteeism and disability. Increases lifespan so people work longer

1 The total value net of drug costs of five best-in-class innovative drugs are between1,300 bn to 1,500 bn JPY

Disease	Case study drug	Sources of value	Included patients	Value Billion JPY
 COPD	SPIRIVA (tiotropium)	▪ Slow down progression of disease if treatment is initiated early when symptoms are still mild	▪ 40-50 years old males and females	~70
 Diabetes	Januvia (phosphate de sitagliptine)	▪ Enhanced reduction in HbA1c resulting in less incidence of various diabetic complications; no hypoglycemia	▪ 40-70 years old males and females	35~138
 Stroke prevention in AF	Eliquis® (apixaban) tablets	▪ Compared to warfarin, lower incidence of stroke, intracranial hemorrhage and all-cause mortality	▪ 40+ years old males and females	1,050
 Depression	Cymbalta® duloxetine HCl	▪ Increased in remission rate compared to placebo resulting in more patients returning to work and preventing GDP loss	▪ 15-64 years old males and females	80~165
 Chronic kidney disease (CKD)[1]	 Nu Lotan	▪ Mean arterial BP reduction and renal protective effect delay the need for dialysis and reduce incidence of other complications such as renal transplant	▪ 50-69 years old males only	~80

Additional value of 626 bn JPY if productive age increases from 65 to 70

~1,300-1,500 bn JPY

1 For CKD caused by diabetic nephropathy only

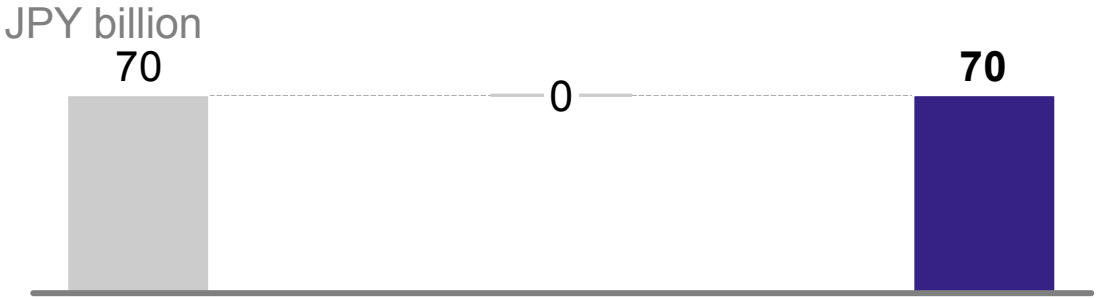
SOURCE: Industry research; Japan clinical data; Literature search; Expert interviews

1 Overview of the value of Spiriva compared with placebo

Applicable population

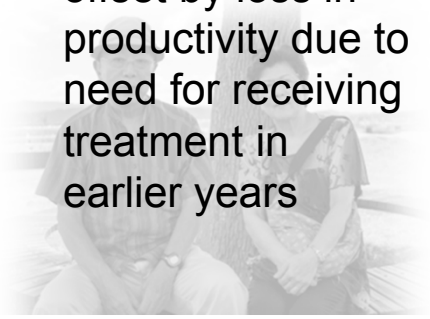
Patients 40-50 years old males and females until death

Value based on the applicable population



- Slow down pro-gression of COPD

- Preservation of productivity in later years is offset by loss in productivity due to need for receiving treatment in earlier years



SOURCE: 1 Salmeterol and Fluticasone Propionate and Survival in Chronic Obstructive Pulmonary Disease, February 22, 2007, Peter M.A. Calverley, et al., N Engl J Med

DIABETES (1 of 2)

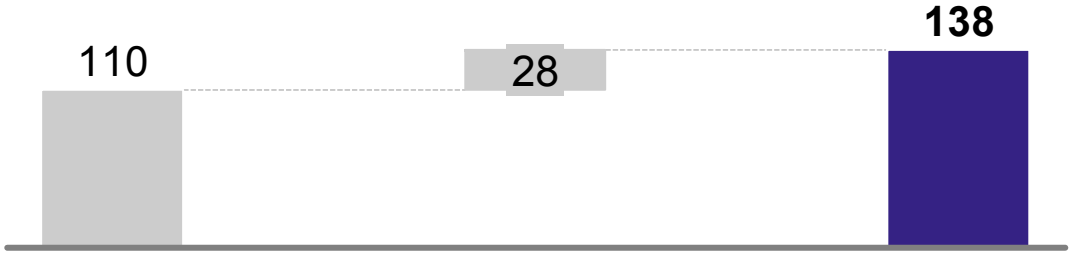
1 Overview of the value of Januvia compared with αGI

Applicable population

Patients 40-70 years old males and females until death

Value based on the applicable population

JPY billion



Cost savings

- Reducing complications from diabetes

Productivity preservation

- Maintaining workforce health level above productivity level

Total value

SOURCE: 1 Relationship between glycated haemoglobin and microvascular complications: Is there a natural cut-off point for the diagnosis of diabetes?, C. Sabanayagam, et al., 2009, Diabetologia
2 Cardiovascular safety of sitagliptin in patients with type 2 diabetes mellitus: a pooled analysis, Engel SS, 2013, Cardiovasc Diabetol
3 Effects of sitagliptin beyond glycemic control: focus on quality of life, Yoshiko Sakamoto, et al., 2013, Cardiovascular Diabetology 2013
4 The association between symptomatic, severe hypoglycaemia and mortality in type 2 diabetes: retrospective epidemiological analysis of the ACCORD study, 2009, Denise E Bonds, et al., BMJ

1 Overview of the value of Januvia + SU compared with SU

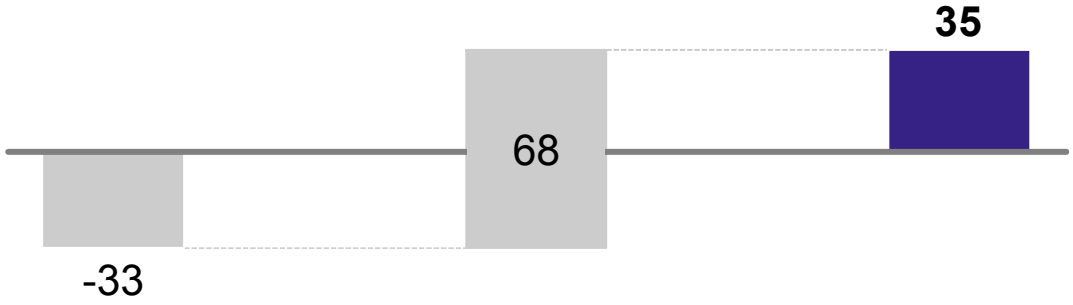
Januvia (phosphate de sitagliptine)

Applicable population

Patients 40-70 years old males and females until death

Value based on the applicable population

JPY billion



Cost savings

- Cost of Januvia as an add-on therapy, net of savings in medical care

Productivity preservation

- Maintaining workforce health level above productivity level

Total value

SOURCE: 1 Relationship between glycated haemoglobin and microvascular complications: Is there a natural cut-off point for the diagnosis of diabetes?, C. Sabanayagam, et al., 2009, Diabetologia
2 Cardiovascular safety of sitagliptin in patients with type 2 diabetes mellitus: a pooled analysis, Engel SS, 2013, Cardiovasc Diabetol
3 Effects of sitagliptin beyond glycemic control: focus on quality of life, Yoshiko Sakamoto, et al., 2013, Cardiovascular Diabetology 2013
4 The association between symptomatic, severe hypoglycaemia and mortality in type 2 diabetes: retrospective epidemiological analysis of the ACCORD study, 2009, Denise E Bonds, et al., BMJ

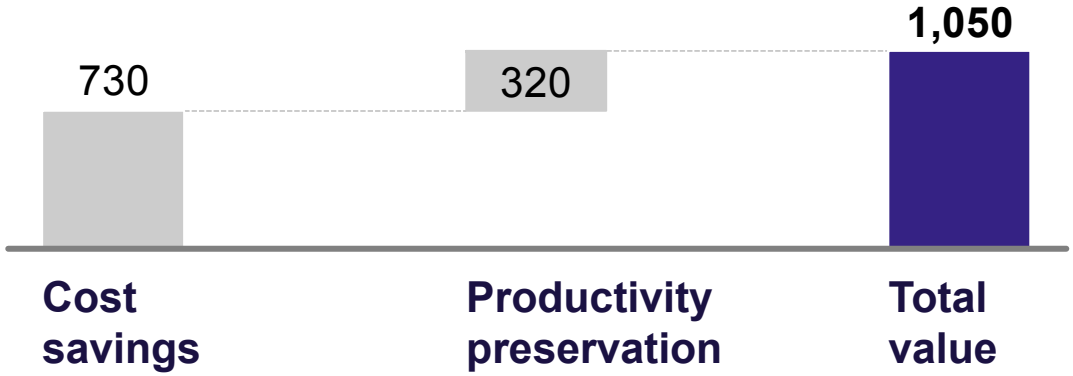
1 Overview of the value of Apixaban compared with Warfain

Applicable population

Patients 40+ years old males and females until death

Value based on the applicable population

JPY billion



- More effectively preventing stroke
- With fewer complications such as bleeding

- Maintaining workforce health level above productivity level

SOURCE: 1 Apixaban versus Warfarin in Patients with Atrial Fibrillation, September 15, 2011, Christopher B. Granger, N Engl J Med
2 Cost-Effectiveness of Apixaban Compared with Warfarin for Stroke Prevention in Atrial Fibrillation, Soyon Lee, et al., 2012, PLOS ONE

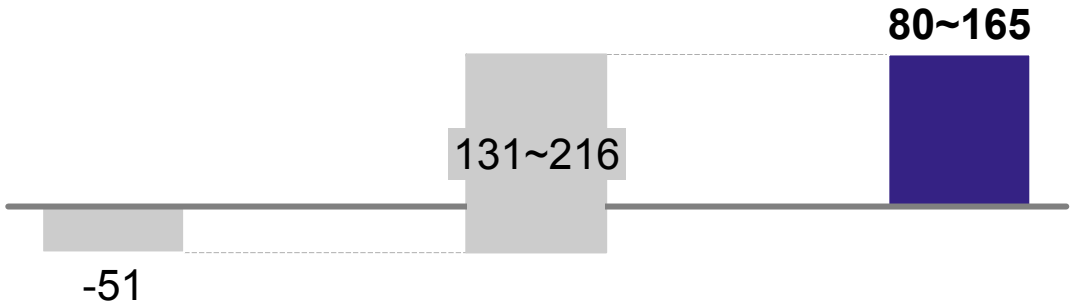
1 Overview of the value of Cymbalta compared with placebo

Applicable population

Patients 15-64 years old males and females until death

Value based on the applicable population

JPY billion

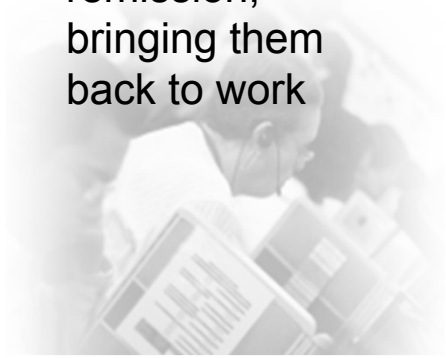


Cost savings

- Cost of Cymbalta, net of savings in medical care and hospitalization costs

Productivity preservation

- Helping more patients achieving remission, bringing them back to work



Total value

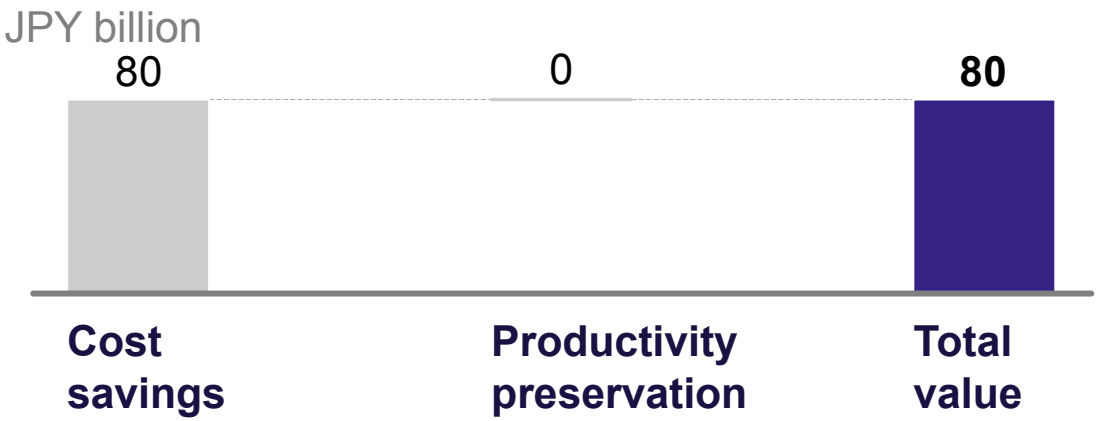
SOURCE: 1. Enhancing Outcomes from Major Depression: Using Antidepressant Combination Therapies with Multifunctional Pharmacologic Mechanisms from the Initiation of Treatment, Stephen M. Stahl, 2010, CNS Spectr; 2. Depression Treatment with Duloxetine and Reduction of Inability to Work, Michael Happich, et al., 2012, Depression Research and Treatment

1 Overview of the value of Nu Lotan compared with placebo

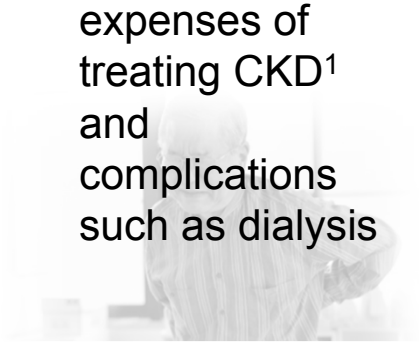
Applicable population

Patients 50-69 years old males only until death

Value based on the applicable population



- Cost savings in drugs, and medical expenses of treating CKD[1] and complications such as dialysis



- No productivity preservation as CKD[1] patients generally pass the productive age

1 Caused by diabetic nephropathy

SOURCE: 1 Effects of Losartan on Renal and Cardiovascular Outcomes in Patients with Type 2 Diabetes and Nephropathy, Barry M. Brenner, et al., September 20, 2001, N Engl J Med
2 Preserving renal function in adults with hypertension and diabetes: a consensus approach. National Kidney Foundation Hypertension and Diabetes Executive Committees Working Group, Bakris GL, et al., 2000, Am J Kidney Dis

1 Enhance quality of life (1 of 3)

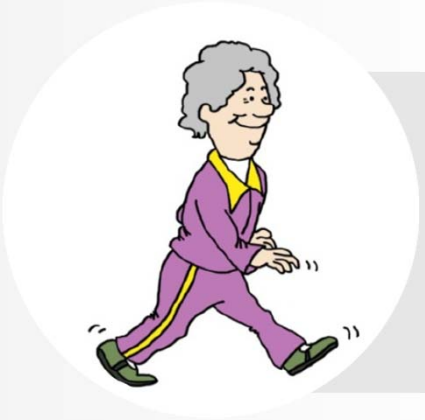
EXAMPLE: **COPD**

COPD PATIENT

- Suffers from shortness of breath and **persistent coughing**
- **Loses ability** to exercise and carry out daily activities
- Spends at least **one month**[1] every year in hospitals

WITH INNOVATIVE DRUGS

Spends quality time with grandchildren every weekend



Takes a stroll at the park five days a week

1 Based on Japan clinical study of COPD patients

SOURCE: MHLW

1 Enhance quality of life (2 of 3)

EXAMPLE: **DEPRESSION**

DEPRESSION PATIENT

- Suffers from **low mood** and **loss of interest** in activities
- Has **pain and suicidal** thoughts
- Average period of absence from work up to **4.8 months**[1]

WITH INNOVATIVE DRUGS

Attends close friends' birthday parties and celebrations once a month

Enjoys family dinners with loved ones every day

1 Based on Japan clinical study of depressive patients

SOURCE: MHLW

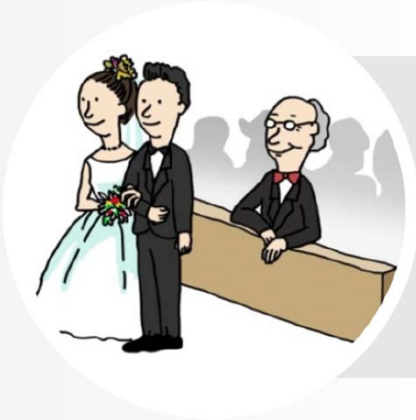
1 Enhance quality of life (3 of 3)

EXAMPLE: **DIABETES**

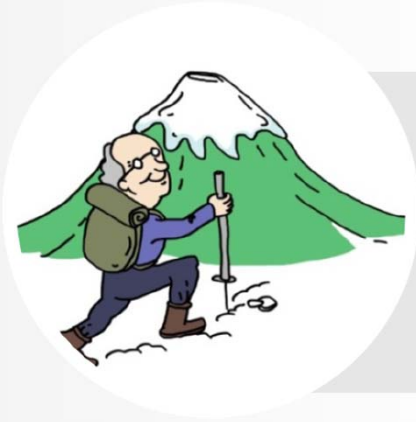
DIABETES PATIENT

- Suffers from complications such as **blindness** and **loss limbs**
- A diabetic nephropathy patient spends on average **two months**[1] every year in hospitals

WITH INNOVATIVE DRUGS



Attends daughter's wedding



Hikes mount Fuji three times a year

1 Based on Japan clinical study of diabetic patients

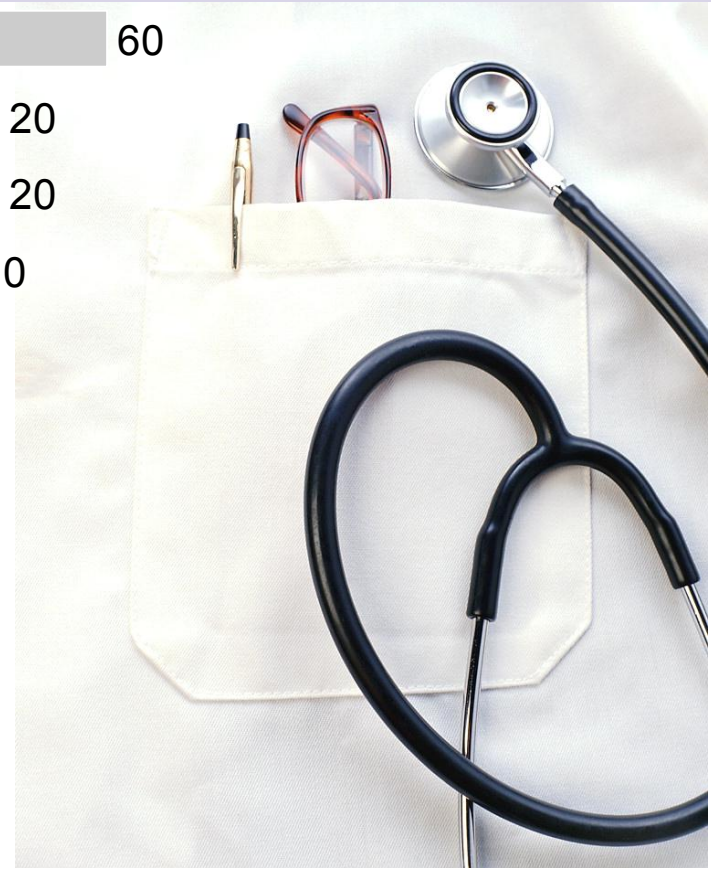
SOURCE: MHLW

2 Healthcare related jobs were the largest contributor to total job adds in Japan in 2011

INDUSTRIES WITH THE MOST JOBS ADDED 2010-11

Healthcare related job adds

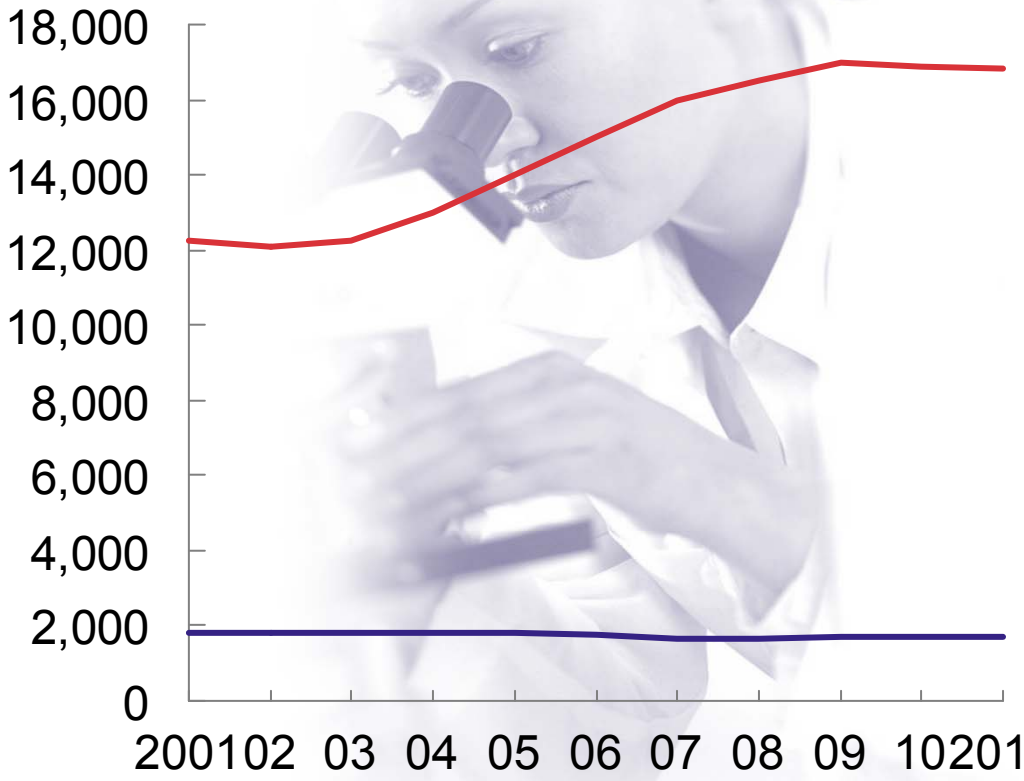
Industry	Number of jobs created (Thousands)
Medical, health and welfare	230
Scientific research, professional & technical	60
Education, learning support	60
Real estate and goods rental and leasing	20
Living-related services	20
Government, except elsewhere classified	10
Mining and quarrying of stone and gravel	0
Construction	0
Fishery	-10
Transport and postal activities	-10
Services, except elsewhere classified	-10
Finance and insurance	-20



SOURCE: Labor force survey by Statistics Bureau of Ministry of Internal Affairs & Communication

3 Having a thriving pharmaceutical industry can attract more scientists with advanced degrees

Number of doctorate in science, 2001-11



2000-10 CAGR
Percent

USA[1] — 3.3

Japan[2] — -0.1

1 Number receiving doctorate degrees
2 Number entering doctorate degrees

SOURCE: Country statistics

4 A direct positive impact of innovation on GDP is export – home grown Japanese medicine has generated sizable exports

Product	Manufacturer	Indication	2012 sales JPY billions	% Sales outside Japan
ABILIFY (aripiprazole)	Otsuka	Antipsychotic	411	94
BLOPRESS®	Takeda	Hypertension	216	38
Takepron OD	Takeda	Gastric and duodenal ulcers	122	37

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Japan’s healthcare is the one of the best in the world, however risks exist that can undermine this system

Investments in healthcare, particularly in innovative medicine can mitigate these risks

The importance of innovative medicine has implications on a number of stakeholders

Japanese government should continue to promote innovation, which will create win-win for the overall Japanese society

Government will get fiscal relief which will in turn benefit the healthcare system

Patients will enjoy better quality of life

Physicians can provide better care solutions for patients

Academia can better attract and develop scientific talent

Overall Japan economy will benefit from GDP and job creation

Appendix

Executive summary (1/3)

1 Japan has been successfully delivering superior healthcare outcomes at moderate cost relative to the OECD peer countries.

However, the emerging demographic and economic risks could undermine Japan's achievements

- **Superior healthcare outcome**
  - Japan demonstrates the best performance in health outcomes
    - Highest life expectancy at birth (83.0 years in 2009)
    - One of the lowest infant and premature mortality
    - Lowest mortality from major disease (e.g., cancer, circulatory diseases, diabetes)
  - Japanese patients enjoy the best physician access and care quality
    - All patients can get same/next-day appoint (e.g., 100% in Japan vs. less than 50% in US in 2012)
    - The lowest in-hospital case-fatality rates within 30 days after admission for ischemic stroke (1.8% in Japan vs. 3.0% in US in 2009)
- Japan has kept the healthcare spending at a moderate level
  - The lowest total healthcare spending as a percentage of GDP (i.e., 9.5% of GDP in 2010)
  - One of the lowest healthcare cost per capita ($34K PPP in Japan vs. $46K PPP in US 2009)
- **Risks that can undermine these achievements:**
  - Growing needs of care for elderlies due to rapidly aging population, e.g., a 65+ year-old patient consumes 132% more spending, 186% more hospitalization day, and 91% more outpatient visit than an average Japanese
  - ~90% of corporate health insurance societies (Kempo Kumiai) suffers from deficits up to JPY 600 billion annual loss in total
  - The implied productivity growth in healthcare under the government's growth plan is significantly higher than the recent slowing trend; thus, more value creation in healthcare is critical to sustain the outcome level
  - Undermined healthcare outcomes could deteriorate the labor productivity and economic growth

Executive summary (2/3)

2 Investments in healthcare, particularly in innovative medicine can provide a virtuous cycle that help mitigate these risks and create significant social and financial benefits

- **Investment in innovative medicine can more effectively treat or prevent diseases, leading to less need for care or hospitalization, particularly for the elderlies**
  - Innovative medicine can, in fact, 1) reduce the life-time cost of treatments and 2) avoid the people's productivity loss, relieving the funding gap
    - For example, a recent analysis of five innovative drugs in major chronic diseases suggests these drugs can bring net value of at least **JPY 1,300-1,500** billion in total
      - Selected Diabetes, COPD, CKD, Stroke prevention in AF and Depression that represent **24%** of total medical expenditures in Japan in 2011
      - The net value is equivalent to **16 %** of total medical expenditures in these five disease areas
      - Also, the net value is more than **twice the funding gap** of the Kempo Kumiai
    - Global clinical data where Japan unique data is not available also indicates **even higher potential value**
    - Similarly, innovative drugs in **other major disease areas** (e.g., oncology, vaccines) should **also bring significant value**
  - Moreover, innovative medicine can also enhance patients' quality of life and create impact that reaches far beyond financial benifits
    - For instance, a typical 65-year old female COPD patient with severe symptoms who is to largely lose her ability even to walk and has to stay home everyday for treatment could delay the progression significantly by an early adoption of innovative drug (e.g. Spiriva) and can spend time with family for outdoor activities
    - Similarly, with innovative medicine, depression patients can achieve remission and enjoy everyday social life; Diabetes patients can carry on with their daily activities normally and not miss important life events, such as annual hiking trips to Mount Fuji and children's wedding

Executive summary (3/3)

2 …continued from above

- **Investment in healthcare and innovative medicine will also generate Indirect but significant impacts for the future growth of Japan**
  - **Job creation:** Labor productivity enhanced by the innovative medicine will drive the overall economic growth and job creation, particularly in the growth sector like healthcare industry
  - **Science talent development:** Japan is facing a decline in "science" background PhDs Investment in healthcare for driving further innovation will drive the talent development platform for scientists
  - **Direct R&D investment:** As the market environment is further friendly to innovation, Japan will get further attention from global companies for investment, including more clinical trials throughout Japan and also more collaborations with Japanese science
  - **Export of Japan-origin innovation:** As the major high-tech manufactures used to be, exports of Japan-origin innovation, including new pharmaceutical materials and finished products, can create future economic gain from overseas (e.g. Blopress from Takeda, and Abilify from Ostuka)

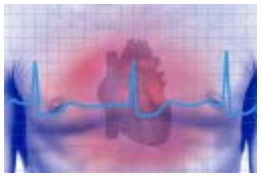
3 Implication to the stakeholders – Investment in healthcare and innovative medicine will bring all "win-win" to the society

- Upfront investment in innovative drugs will benefit all stakeholders embedded in the healthcare system for better outcome and better society
  - **Government** from loosening the fiscal constraints & strains on the healthcare system
  - **Patients** from better quality of life
  - **Physicians** from better care solution for patients
  - **Academia** from enhanced scientific talent development
  - **Overall economy** from GDP and job creation
  - **The entire Japan as country** from the enhanced Japanese players' global presence and the attention from global companies
- To achieve this all "win-win" to the society, Japanese government should continue to encourage and facilitate the innovation in healthcare and pharmaceuticals

Value of medicine by disease area

COPD

Diabetes



Stroke prevention in AF

Depression

CKD

COPD

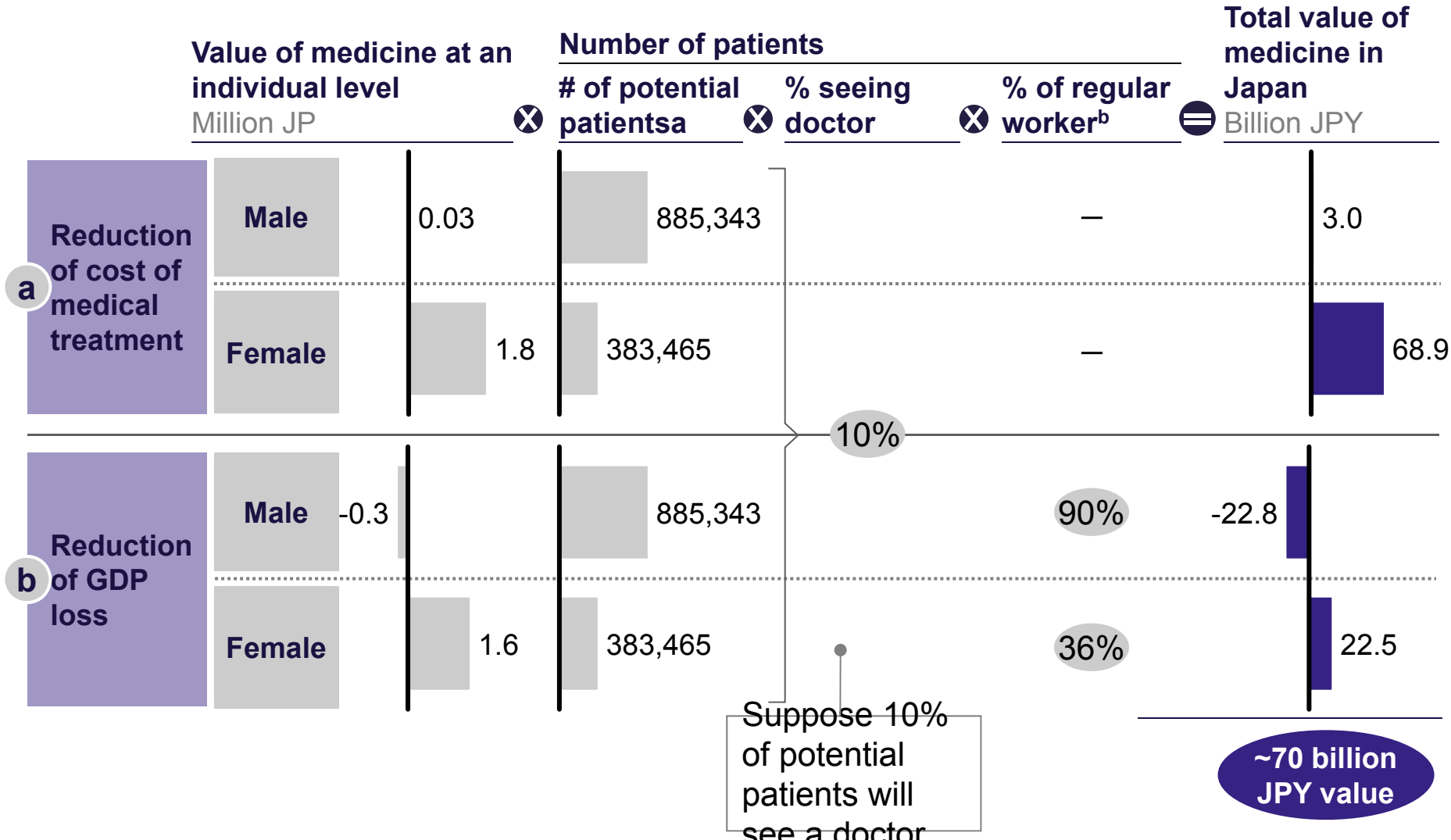
Key drivers of the value of Spiriva

		Japanese data available	Included in sizing	Global data available
Efficacy in managing core COPD symptoms and slowing down disease progression		✓	✓	✓[1]
Efficacy in preventing complications such as heart disease		✗	✗	?
Minimizing side effects compared with other therapy (e.g., anticholinergic side effects)		✗	✗	?
Others	Impact on GDP as a result of slowing down disease progression	✓	✓	✓[1]
	Reduction in family burden as a result of better disease management	✗	✗	?
	Improved quality of life	✗	✗	✓

SOURCE: 1 Salmeterol and Fluticasone Propionate and Survival in Chronic Obstructive Pulmonary Disease, February 22, 2007, Peter M.A. Calverley, et al., N Engl J Med

COPD – Population level

Overview of value of COPD medicine at the population level



a Calculated by multiplying the number of potential patients by % of each sex and % of patients whose ages are between 40 and 50, based on the data from a clinical study and MHLW..
b Calculated with the number of regular worker and the number of people in the age group (40-50).

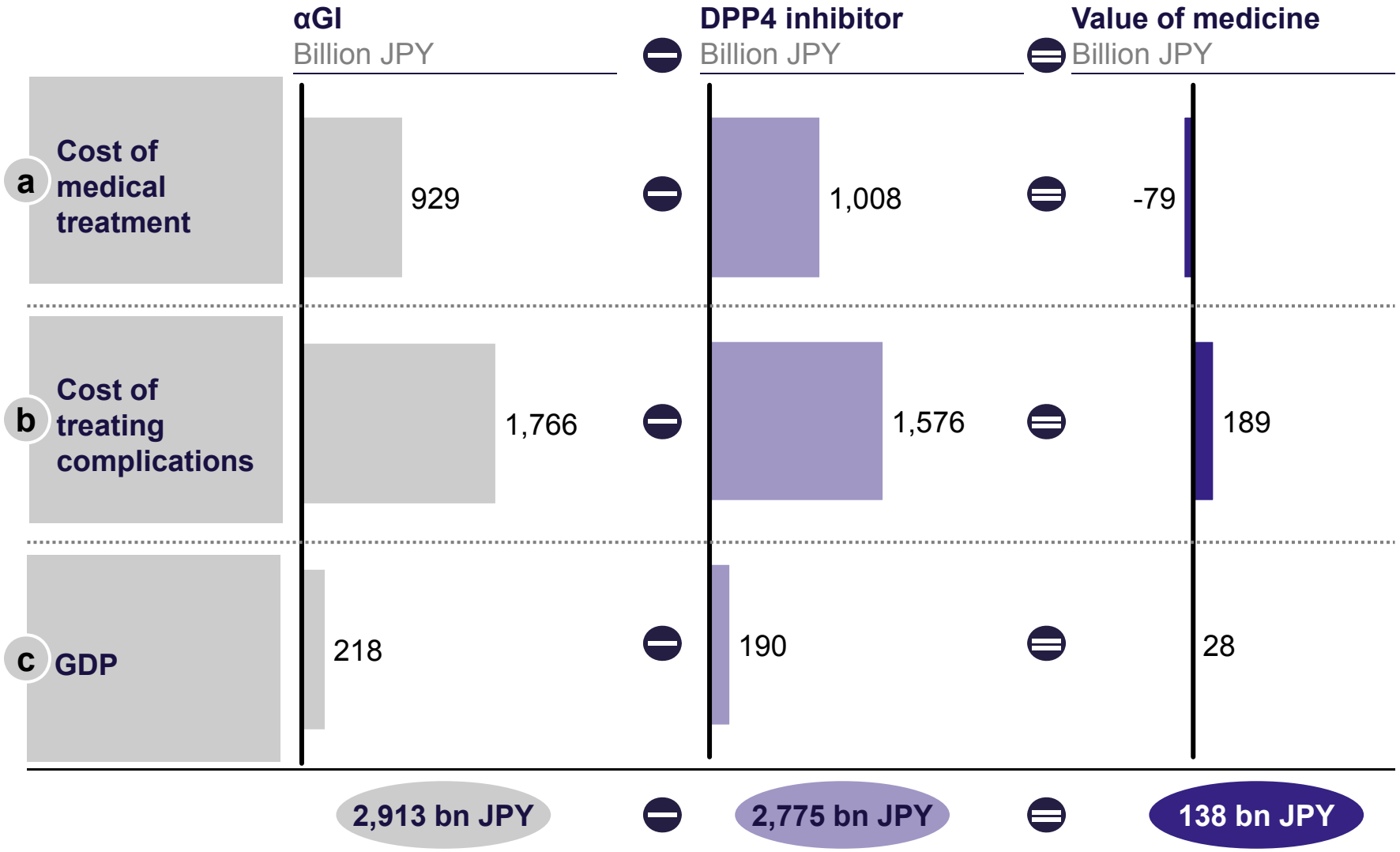
SOURCE: 「平成23年度国民経済計算確報 (フロー編)」,「第1回今後のパートタイム労働対策に関する研究会　配付資料 資料4　パートタイム労働の現状, Labor Force Survey, Historical data 1 (2) Employed person (by age group) - Whole Japan, Monthly Data, Table 4 on MHLW's website regarding working hours (http://www.mhlw.go.jp/toukei/itiran/roudou/jikan/syurou/11/gaiyou01.html), UPLIFT study (http://www.uplift-study.com/ers2009/doc1.html),「日本における慢性閉塞性肺疾患の医療経済評価モデルの構築と新規COPD治療薬チオピトロウムの費用効用分析」 Prevalence of chronic obstructive pulmonary disease in Japan : results from the NIPPON COPD epidemiology(NICE)study, Population Survey Report, 「第1回今後のパートタイム労働対策に関する研究会　配付資料 資料4　パートタイム労働の現状,「平成23年パートタイム労働者総合実態調査の概況：個人調査」, Patient research

Key drivers of the value of Januvia

		Japanese data available	Included in sizing	Global data available
Efficacy in managing blood glucose / reducing diabetic complications compared with diet + exercise and standard therapy	Retinopathy	✓	✓	✓ [1] Relationship between HbA1c and prevalence rate
	Nephropathy	✓	✓	✓ [1] Relationship between HbA1c and prevalence rate
	Cardiovascular diseases (CVD)	✓ For ischemic heart disease only	✓ For ischemic heart disease only	✓ [2]
	Neuropathy	✗	✗	✓ [1] Relationship between HbA1c and prevalence rate
Other pharmacological effects such as improvement in blood pressure or lipids		✓ Limited [3]	✗ Single-arm, non-comparison and small sample study	✓
Minimizing side effects compared with current therapy	Hypoglycemia leading to complications such as mortality	✗	✗	✓ [4]
	Weight gain	✓ Limited [3]	✗	✓
Others	Impact on GDP as a result of diabetic complications	✓ For the 3 compli-cations stated above	✓ For the 3 compli-cations stated above	✓ [1,2]
	Improved compliance due to once-a-day dosing	✗	✗	?
	Reduction in family burden as a result of better disease management	✗	✗	?
	Improved quality of life	✓ Limited [3]	✗ Single-arm, non-comparison and small sample study	✓

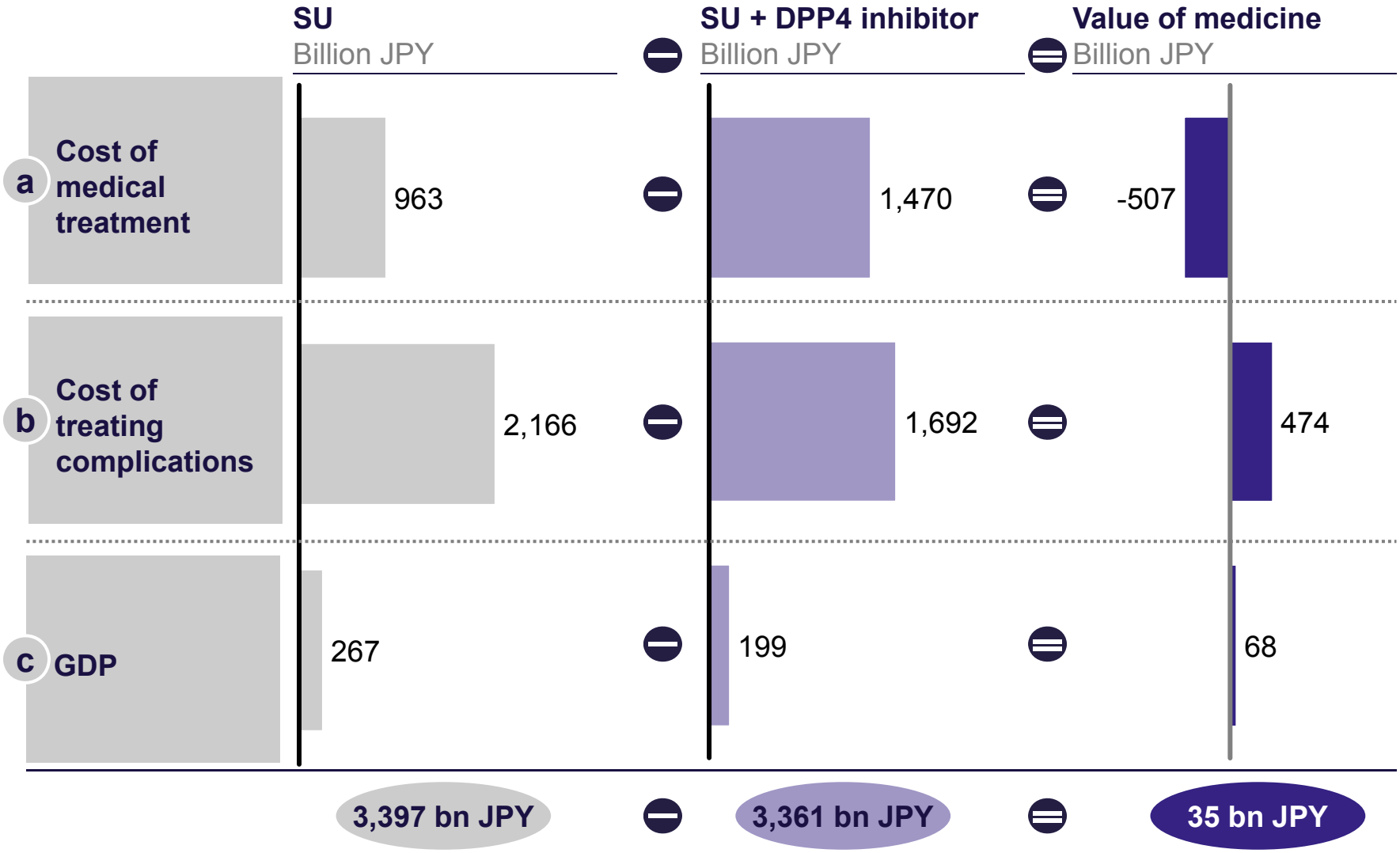
SOURCE: 1 Relationship between glycated haemoglobin and microvascular complications: Is there a natural cut-off point for the diagnosis of diabetes?, C. Sabanayagam, et al., 2009, Diabetologia
2 Cardiovascular safety of sitagliptin in patients with type 2 diabetes mellitus: a pooled analysis, Engel SS, 2013, Cardiovasc Diabetol
3 Effects of sitagliptin beyond glycemic control: focus on quality of life, Yoshiko Sakamoto, et al., 2013, Cardiovascular Diabetology 2013
4 The association between symptomatic, severe hypoglycaemia and mortality in type 2 diabetes: retrospective epidemiological analysis of the ACCORD study, 2009, Denise E Bonds, et al., BMJ

Overview of value of DPP4 inhibitor compared with αGI at the population level



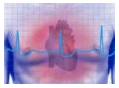
SOURCE:「最新　医療費の基本と仕組みがよ～くわかる本「[第3版]」,「糖尿病になったらいくらかかる？」, Website of "Diabetes Net" (http://www.dm-net.co.jp/seido/02/),「今日の治療薬 2013」, Website of 平成24年調剤報酬表 (http://www1.ocn.ne.jp/~kaminote/houshuuhyou.html), メディファーマ, Incidence and progression of diabetic retinopathy in Japanese adults with type 2 diabetes: 8 year follow-up study of the Japan Diabetes Complications Study (JDCS),「糖尿病の医療費分析報告」, Website of Aso city(http://www.city.aso.kumamoto.jp/living/health/welfare/13-1.html#02), Low transition rate from normo- and low microalbuminuria to proteinuria in Japanese type 2 diabetic individuals: the Japan Diabetes Complications Study (JDCS),「JDCS (Japan Diabetes Complications Study) 疫学研究・大規模臨床試験より得られたESM」,「糖尿病と冠動脈疾患の疫学」, What is retinopathy of diabetes?", Website of Lions club international (http://www.lionsclubs.gr.jp/eye-health/e1/e1-2/kenko2.html), Patient research,「ケアネット白書2012 糖尿病編」,

Overview of value of DPP4 inhibitor + SU compared with SU alone at the population level



SOURCE: 「最新　医療費の基本と仕組みがよ～くわかる本「[第3版]」,「糖尿病になったらいくらかかる？」, Website of "Diabetes Net" (http://www.dm-net.co.jp/seido/02/),「今日の治療薬 2013」, Website of 平成24年調剤報酬表 (http://www1.ocn.ne.jp/~kaminote/houshuuhyou.html), メディファーマ, Incidence and progression of diabetic retinopathy in Japanese adults with type 2 diabetes: 8 year follow-up study of the Japan Diabetes Complications Study (JDCS),「糖尿病の医療費分析報告」, Website of Aso city(http://www.city.aso.kumamoto.jp/living/health/welfare/13-1.html#02), Low transition rate from normo- and low microalbuminuria to proteinuria in Japanese type 2 diabetic individuals: the Japan Diabetes Complications Study (JDCS),「JDCS (Japan Diabetes Complications Study) 疫学研究・大規模臨床試験より得られたESM」,「糖尿病と冠動脈疾患の疫学」, What is retinopathy of diabetes?", Website of Lions club international (http://www.lionsclubs.gr.jp/eye-health/e1/e1-2/kenko2.html), Patient research,「ケアネット白書2012 糖尿病編」,

Among the value drivers for Apixaban, improved efficacy on stroke prevention and less bleeding incidence are key



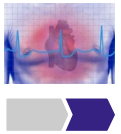
Value drivers included in assessment

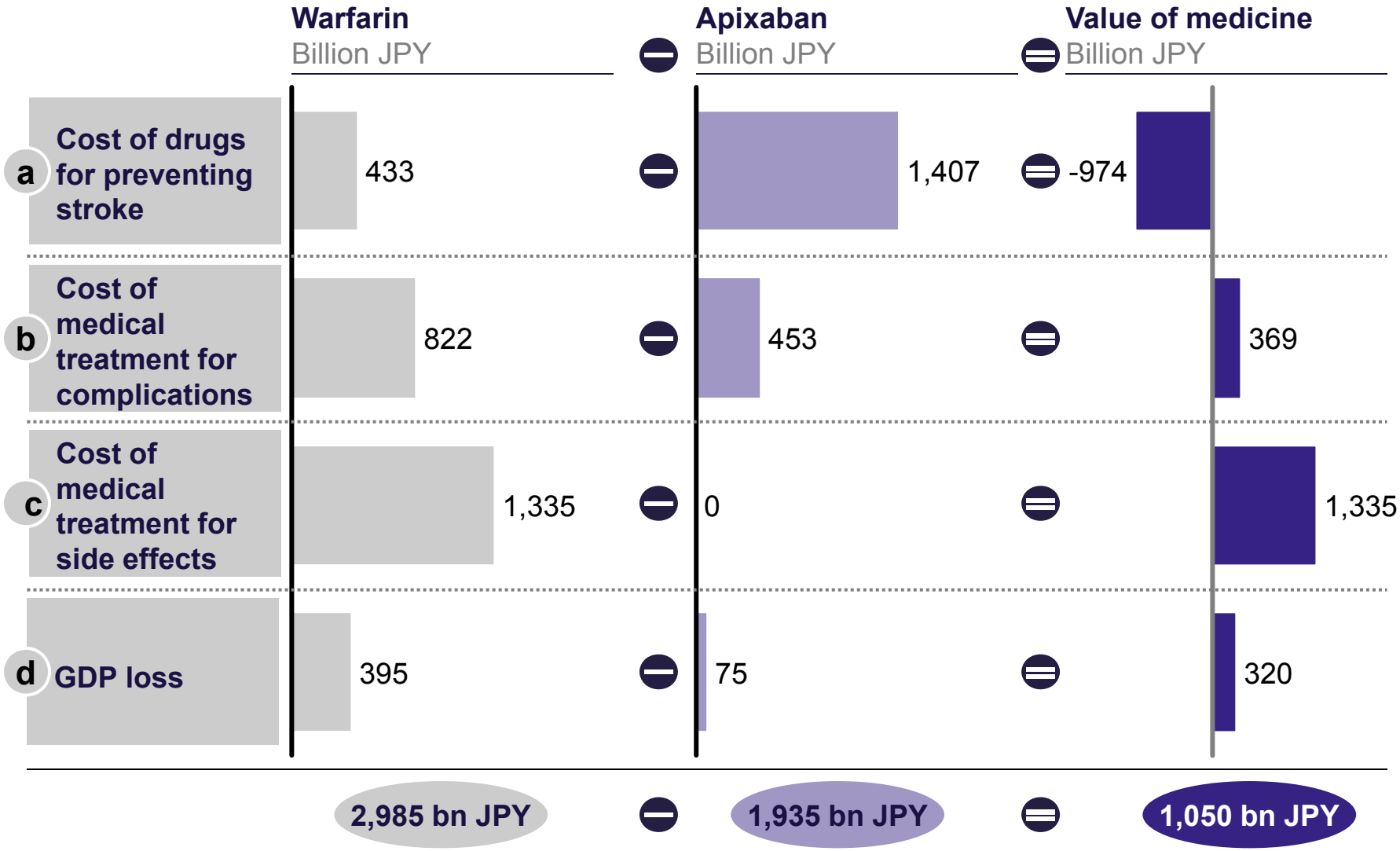
		Japanese data available	Included in sizing	Global data available
Efficacy of drugs compared with warfarin	Preventing stroke and other embolistic events	✓	✓	✓[1]
	Reducing need for monitoring and lab tests	✓	✓	✓[2]
Minimizing side effects compared with warfarin	Intracranial hemorrhage	✓	✓	✓[1]
	Other hemorrhage such as GI bleed	✘	✘	✓[1]
Others	Impact on GDP as a result of disease complications and drug-related side effects	✓ For stroke and intracranial hemorrhage	✓ For stroke and intracranial hemorrhage	✓[1]
	Reduction in family burden as a result of better disease management	✘	✘	?
	Reduction in diet restriction	✘	✘	✓[2]
	Improved quality of life	✘	✘	✓[2] Cost effectiveness measured by QALY

SOURCE: 1 Apixaban versus Warfarin in Patients with Atrial Fibrillation, September 15, 2011, Christopher B. Granger, N Engl J Med
2 Cost-Effectiveness of Apixaban Compared with Warfarin for Stroke Prevention in Atrial Fibrillation, Soyon Lee, et al., 2012, PLOS ONE

STROKE PREVENTION IN AF – Population level

Overview of value of Apixaban compared with Warfarin at the population level





SOURCE: Prevalence of atrial fibrillation in the general population of Japan: An analysis based on periodic health examination, 2009, Inoue H, et al: Int J Cardiol 137; Population Survey Report, Table 3-2 and 3-3 of Appendix of Volume 1, 2011, MHLW; Prevalence clinical characteristics of patients with atrial fibrillation – Analysis of 20,000 cases in Japan-, 2000, Tomita F, et al: Jpn Circ J; Can the relationship between endothelial function and CHADS2 score account for the pathogenesis of thromboembolism?, Terazawa H, et al,「脳卒中患者の生命予後と死因の5年間にわたる観察研: 栃木県の調査結果とアメリカの報告との比較」

DEPRESSION

Key drivers of the value of Cymbalta

		Japanese data available	Included in sizing	Global data available
Efficacy of Cymbalta compared with placebo	Achieving remission	✓	✓	✓
	Second relapse after initial remission	✓	✓	✓[1]
	Hospitalization	✗	✓	✓
	Suicidal rate	✓ Data on SSRI only	✗	✓
Minimizing side effects compared with placebo		✓	✓	✓
Others	Impact on GDP as a result of depression	✓	✓	✓[2] Effect of Cymbalta on ability to work
	Reduction in family burden as a result of better disease management	✗	✗	?
	Improved quality of life	✗	✗	?

SOURCE: 1. Enhancing Outcomes from Major Depression: Using Antidepressant Combination Therapies with Multifunctional Pharmacologic Mechanisms from the Initiation of Treatment, Stephen M. Stahl, 2010, CNS Spectr; 2. Depression Treatment with Duloxetine and Reduction of Inability to Work, Michael Happich, et al., 2012, Depression Research and Treatment

DEPRESSION – Population level

Overall value of Cymbalta compared to placebo at population level

Value of Cymbalta compared to placebo at individual level
Thousand JPY

Value of Cymbalta compared to placebo at population level
Billion JPY

Cost of treating depression (Direct cost)

-102

-51

GDP loss (Indirect cost)

499-873

134～217

Medical treatment cost for side effects

~0

~0

80~165 bn JPY

If the productive age is extended from 65 to 70, the GDP impact will become 194-314 bn JPY, and the total impact will become ~140-260 bn JPY

SOURCE: 「精神障害による休業者に関する調査 」, Table 4 on MHLW's website regarding working hours (http://www.mhlw.go.jp/toukei/itiran/roudou/jikan/syurou/11/gaiyou01.html),「平成23年度国民経済計算確報 (フロー編)」,「第1回今後のパートタイム労働対策に関する研究会　配付資料 資料4　パートタイム労働の現状, Labor Force Survey, Historical data 1 (2) Employed person（by age group） - Whole Japan, Monthly Data, Patient research,「病気にかかるおカネ」,「今日の治療薬 2013」,うつ病の病態・診断・治療, (http://www-yaku.meijo-u.ac.jp/Research/Laboratory/chem_pharm/09jugyou/101203lecture.pdf),「Duloxetineの特徴 – 国内第3相比較試験の再解析結果を中心に - 」,「Duloxetineの大うつ病性障害に対する臨床評価- Placebo及びparoxetineを対象薬とした二重盲検比較試験 -」,「うつ病の長期経過」

CKD

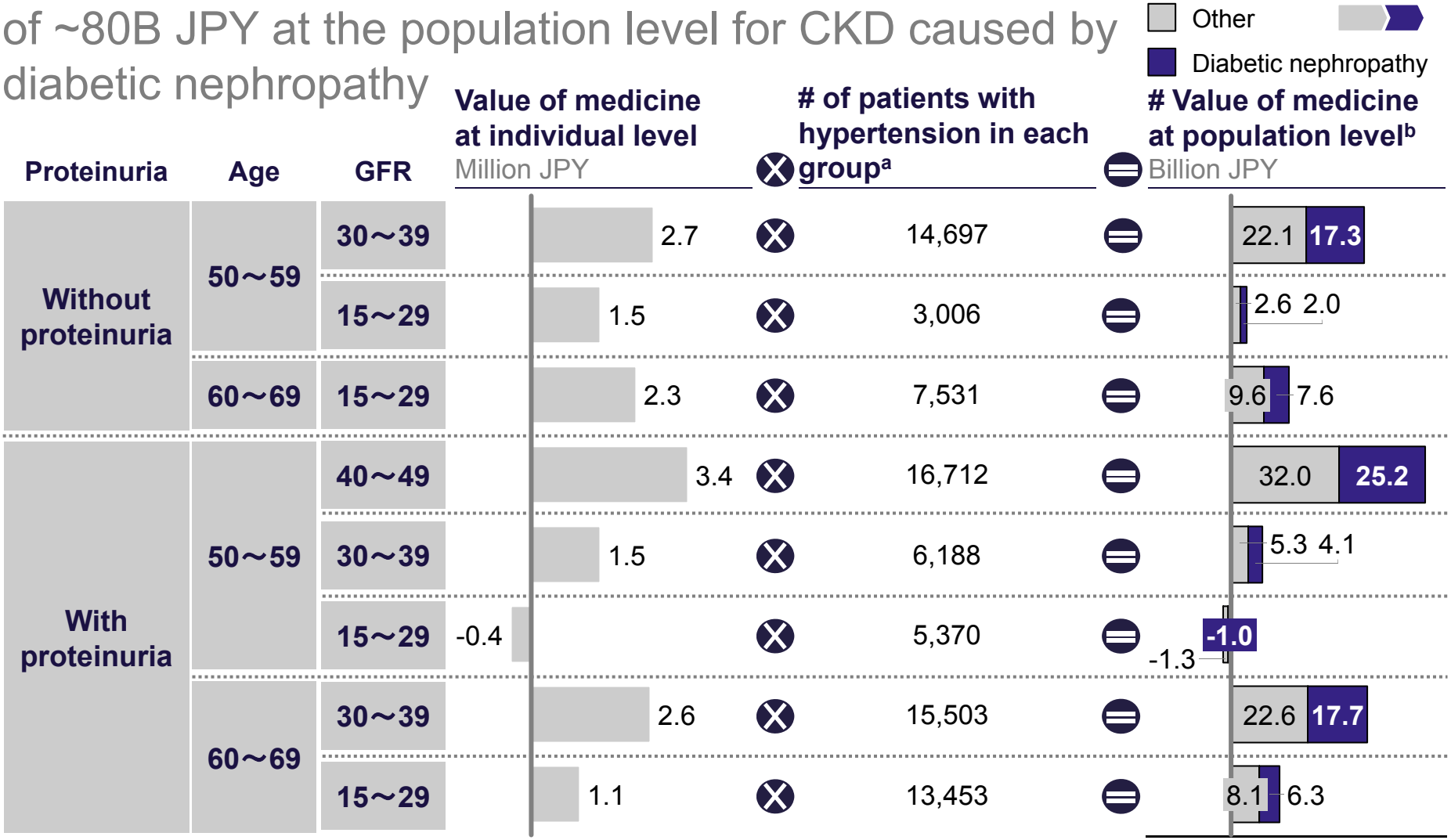
Key drivers of the value of Nu Iotan

		Japanese data available	Included in sizing	Global data available
Efficacy of drugs compared with placebo for other CKD / non-diabetic nephropathy patients	Reducing blood pressure	✓	✓	✓ [1]
	Reducing the speed of GFR decline by reducing blood pressure	✓	✓	✓ [2]
	Other renal-protective effects (e.g, reducing proteinuria)	✓	✓	✓ [1]
	As a result of the above, reduction in ESRD and mortality	✓	✓	✓ [1]
Efficacy of drugs in reducing other complications such as CVD		✗	✗	?
Others	Impact on GDP as a result of disease complications	✓	✗ Because most patients already passed the productive age	✓ [1]
	Reduction in family burden as a result of better disease management	✗	✗	?
	Improved quality of life	✗	✗	?

SOURCE: 1 Effects of Losartan on Renal and Cardiovascular Outcomes in Patients with Type 2 Diabetes and Nephropathy, Barry M. Brenner, et al., September 20, 2001, N Engl J Med
2 Preserving renal function in adults with hypertension and diabetes: a consensus approach. National Kidney Foundation Hypertension and Diabetes Executive Committees Working Group, Bakris GL, et al., 2000, Am J Kidney Dis

CKD – Population level

Compared with placebo, Nu Lotan is estimated to deliver a value of ~80B JPY at the population level for CKD caused by diabetic nephropathy



~80 bn JPY

a Calculated by multiplying # of patients in each age group by the percentage of each GFR group first based on data from MHLW1 and Japanese Society[2] of Nephrology, then used percentage of hypertensive patients and patients with proteinuria from a clinical test[3]

b. Calculated based on epidemiology data that 44% of new ESRD patients are caused by diabetic nephropathy, Japan Society of Dialysis Therapy

SOURCE:
1 Population Survey Report, Table 3-2 and 3-3 of Appendix of Volume 1, 2011, MHLW
2 「CKD診療ガイド 2012」, 日本腎臓学会、東京医学社
3 Risk factor profiles based on estimated glomerular filtration rate and dipstick proteinuria among patients of the Specific Health Check and Guidance System in Japan 2008, 2012, Kunitoshi Iseki, et. Al, Clin Exp Nephrol