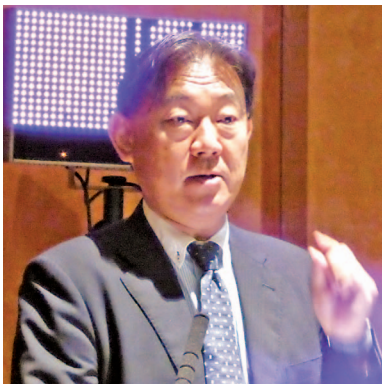
Keynote Lecture 2

Future of health-related biotechnology in Japan *1



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1. Overview of Japan's healthcare challenge

It's my great privilege to address to all of you about the Japan's healthcare challenge, especially with a view to how to promote biotechnology in healthcare. This graph indicates the healthcare expenditure cost for Japan over the years (Fig. 1). It's about $420 billion per year. The average growth rate of the healthcare expenditure is around 2～3%, but we do have a problem here. This is premium paid, copayment and benefits received by each age group (Fig. 2). If you see age 20 to age 60, that's the productive years, the premiums are larger than the benefits, but for the rest of the lives, the benefits are much, much larger than the premium. That's why we have the deficit in healthcare expenditure. The premiums paid by the insured, individual, and the employer is about half of the healthcare expenditure, and out-of-pocket payment, on-spot, of healthcare institution is about 12% (Fig. 3). But we have the deficit of around 40%, so that's the subsidy by the government.

You might be aware that we do have the universal health coverage. But one thing I would like to highlight is the copayment is around 30%, but there is a monthly ceiling to that amount of about $800. Nobody in this country have to pay beyond $800 per month for healthcare, even though you receive very high cost of surgical operations or pharmaceuticals. That's a very good point, but we do have one caution. This is a comparison of the cost performance of the social security cost, by the OECD (Organisation for Economic Co-operation and Development) (Fig. 4). In the x-axis, we have the ageing population ratio; in the y-axis, we have the social security cost divided by national income. As your population ages, the cost will increase. Most of the countries go around this slope, but for Japan, you have very much an aged population, but in terms of cost, it is less than half of the average of the OECD countries. I do believe that Japanese healthcare, pension, and social security

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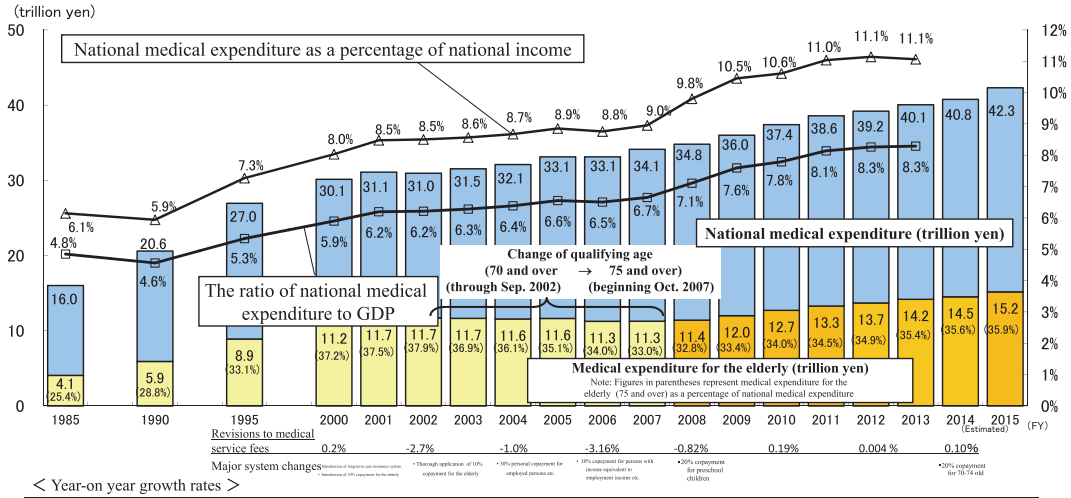
Fig. 1　Trends in health expenditure



< Year-on year growth rates >

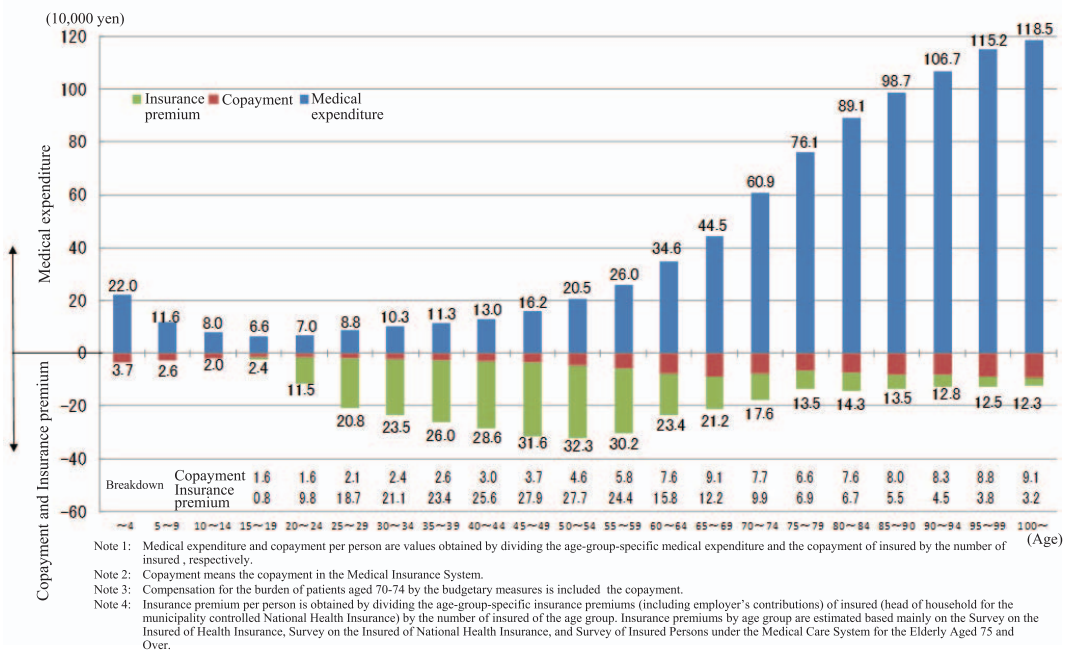
	1985 (S60)	1990 (H2)	1995 (H7)	2000 (H12)	2001 (H13)	2002 (H14)	2003 (H15)	2004 (H16)	2005 (H17)	2006 (H18)	2007 (H19)	2008 (H20)	2009 (H21)	2010 (H22)	2011 (H23)	2012 (H24)	2013 (H25)	2014 (H26)	2015 (H27)
National medical expenditure	6.1	4.5	4.5	−1.8	3.2	−0.5	1.9	1.8	3.2	−0.0	3.0	2.0	3.4	3.9	3.1	1.6	2.2	*1.8*	*3.8*
Medical expenditure for the elderly (75 and over)	12.7	6.6	9.3	−5.1	4.1	0.6	−0.7	−0.7	0.6	−3.3	0.1	1.2	5.2	5.9	4.5	3.0	3.6	*2.3*	*4.6*
National income	7.2	8.1	1.1	1.7	−2.2	−0.8	1.2	0.5	1.1	1.1	0.8	−6.9	−3.0	2.4	−0.9	0.7	2.9	–	–
GDP	7.2	8.6	1.8	0.8	−1.8	−0.7	0.8	0.2	0.5	0.7	0.8	−4.6	−3.2	1.3	−1.3	0.1	1.8	–	–

(%)

Note 1: National income and GDP are from "National economic accounting" published by Cabinet Office. Being used to compare the medical expenditure among OECD countries, total healthcare expenditure is a type of medical expenditure which covers wider areas such as preventative services and so on. The ratio of average medical expenditure of OECD countries to GDP was 9.3% in 2012.

Note 2: The national medical expenditure for FY2013 (and medical expenditure for the latter-stage elderly people (75 and over)) is an estimate. The estimate for FY2013 is made by multiplying the FY2012 national medical expenditure by the growth rate of the rough estimate of FY2013 medical expenditure (stated above in italics).

Fig. 2　Annual medical expenditure, copayment, and insurance premiums per person between age groups (Estimates based on records in FY2010)



Note 1: Medical expenditure and copayment per person are values obtained by dividing the age-group-specific medical expenditure and the copayment of insured by the number of insured , respectively.

Note 2: Copayment means the copayment in the Medical Insurance System.

Note 3: Compensation for the burden of patients aged 70-74 by the budgetary measures is included the copayment.

Note 4: Insurance premium per person is obtained by dividing the age-group-specific insurance premiums (including employer's contributions) of insured (head of household for the municipality controlled National Health Insurance) by the number of insured of the age group. Insurance premiums by age group are estimated based mainly on the Survey on the Insured of Health Insurance, Survey on the Insured of National Health Insurance, and Survey of Insured Persons under the Medical Care System for the Elderly Aged 75 and Over.

Note 5: The figures may not add up due to the rounding of fractions.

Fig. 3 Universal health insurance system

○ Our country has realized the world's longest life expectancy and healthcare standards through the universal health insurance system.
○ It is necessary to ensure a safe and secure living of the citizens continuously by firmly maintaining the universal health insurance with the current social insurance system.

[Characteristics of Japanese universal health insurance system]

1. Covering all citizens through public health insurance
2. Freedom of choice of medical institution (free access)
3. High-quality medical services with low costs
4. While the social insurance system is the basis, the public subsidy is put as resource to maintain the universal health insurance

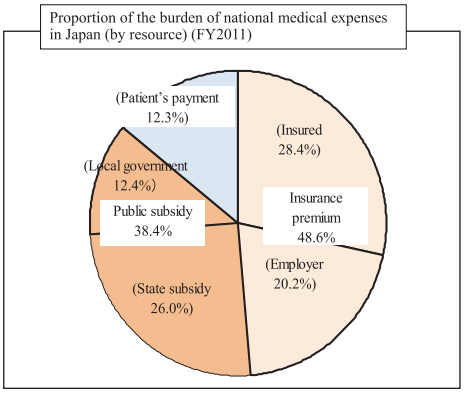
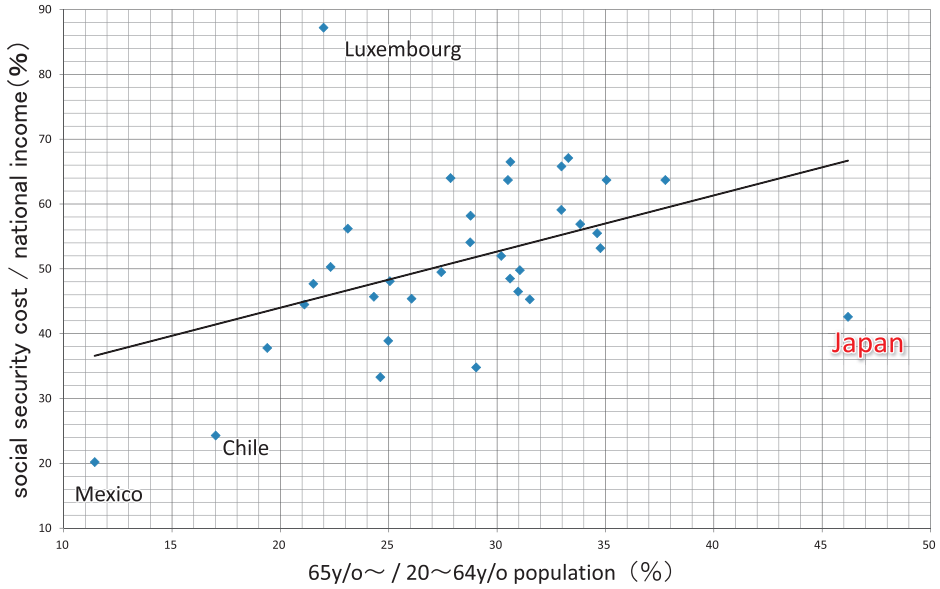


Fig. 4 OECD Comparison: social security cost vs ageing ration



system has a very high cost performance.

In addition to that, this is the kind of outcome of healthcare in Japan. We can see the age-standardized mortality from three major diseases by WHO (World Health Organization): heart attack, cancers, and strokes. For Germany, it is around 296 and Japan is 181, per 100,000. This is by OECD, the people with obesity measured by BMI. If you compare United States (U.S.) and Japan, for U.S., about one-third of the population is obese, but for Japan, it's only 3%. This is the health system outcomes by OECD in terms of life-expectancy at the

age of 65. Japan's life expectancy at 65 years is much longer than other major industrialized countries, but women are always living longer than men. They are much stronger. This is the comparison of quality of healthcare between Japan and the U.S., in terms of registrations in NCD (National Clinical Database) in Japan and NSQIP (American College of Surgeons National Surgical Quality Improvement Program) in the U.S. (Table 1). Japan is covering almost all hospitals and the U.S. about 100 top U.S. hospitals. At the top, we have the liver resection, either laparoscopic approach or open surgery; at the bottom, you have colectomy. Here again you have laparoscopic and open surgery approach. If you compare the U.S. and Japan for mortality after surgery, it's about three times larger

Table 1　Comparison of quality of healthcare between Japan and U.S.

	US / NSQIP (2011-2012)		Japan / NCD (2011-2012)	
LAR (Lower Anterior Resection)	Total = 13989		Total = 37161	
Surgical Approach	Total (%)	Died (%)	Total (%)	Died (%)
Laparoscopic Approach	44.20%	0.71%	42.9%	0.24%
Open Surgery	55.80%	1.37%	57.1%	0.50%
Right hemi-colectomy	Total = 31571		Total = 38740	
Surgical Approach	Total (%)	Died (%)	Total (%)	Died (%)
Laparoscopic Approach	56.9%	0.91%	36.6%	0.31%
Open Surgery	43.1%	3.97%	63.4%	1.02%

in the U.S.. I am convinced that I am staying here in this country if I have liver cancer or colon cancer.

2. Restructuring Japan's healthcare

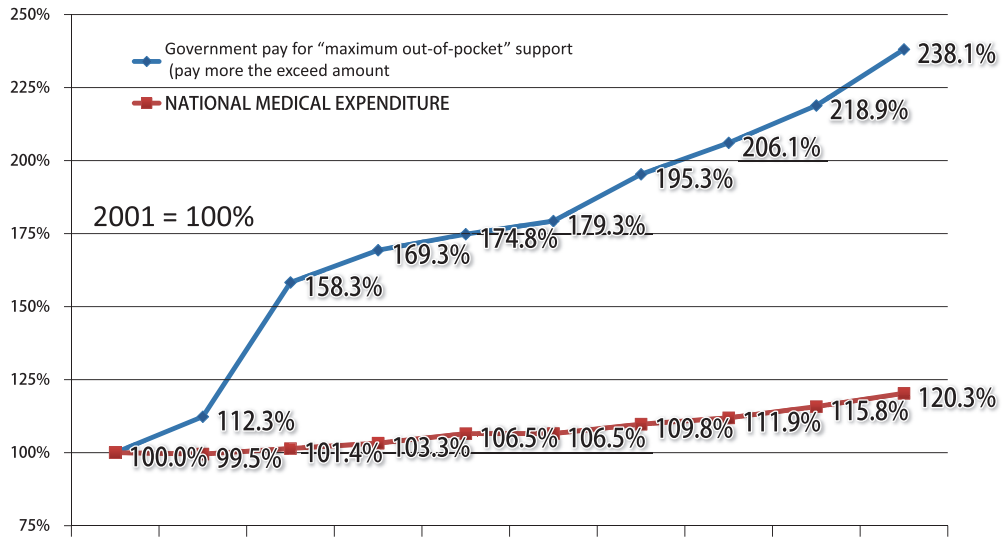
But our healthcare has several problems. One is about human resources. If you compare the number of physicians per 1,000 population in the world, Japan's is not the highest but just below the average. But if you compare the number of clinicians per 100 hospital beds, Japan is about one-fifth of the U.S.. Why this is happening? It's very simple arithmetic. Because the number of beds is about four times larger in Japan, so medical doctors are thinly deployed across hospitals. That's why the M.D.s in this country are very busy.

Next we can see the number of very expensive medical devices per population, CT and MRI, comparing the OECD countries. If you compare the averages between OECD and Japan, for both CT and MRI, Japan has perhaps three or four times CTs and MRIs per population. This is the outpatient. As for the number of average per year, annual visit outpatient in Japan is about 13 times per person as compared to 6.5 OECD average. This is about the cost per outpatient. For Japan, it's less than half as compared to OECD average. If you multiply the number of visits by the cost per visit, total outpatient expenditure might be similar to OECD average, but for Japan, it's more less-expensive visit in this country.

3. Cost-effectiveness analysis for drugs and devices

I told you that we have per-month ceiling of out-of-pocket payment of healthcare. That's a good point but that is leading to one problem (Fig. 5). If you compare the healthcare expenditure between 2001 to 2010, the cost increase is about 20%, almost 2% per year, but if you see the government payment, because people pay up until $800, above that all being paid by the government, the government payment for that above exceeding amount is increasing by 140%, seven times larger than the average healthcare expenditure. That's why we are trying to introduce the cost-effectiveness analysis. But the difference between our system and United

Fig. 5 Government burden for "maximum out-of-pocket" support (Growth)



Kingdom (U.K.) NICE (National Institute for Health and Care Excellence) system, we are introducing ex post system as opposed to ex ante system. For U.K., the cost effective analysis will be done before marketization, but we do after marketization. We are picking up the large volume and high cost pharmaceuticals only, so the number of the target will be very limited in this country. That's why we don't target the pharmaceuticals for rare diseases. Even though they might be expensive, but the number prescribed will be limited. We are using this to shift resources from long-listed products and generics to more innovative products.

This is the time frame (Fig. 6). If the patent expires, the generic conversion will happen, but we still have a lot of long-listed products here. We do cost-effective analysis and shift resources from here to more innovative products. Why do we do it? If you look at this graph, this is the generic conversion after the patent expiration. For U.S., it is about 90%; for Europe, it's around 70%; but in this country, it's about 40% as of 2010. Of course, it's becoming much larger. What we are trying to do is to replace the long-listed products with generics by 80% by 2020 (Fig. 7).

4. Economics of pharmaceutical companies

This is the size of the pharmaceutical and medical device companies. If you look up Takeda, the largest in this country, it is about 16th in the world, and for medical devices, Terumo is about 20th. We have rather tiny companies in this country. If you look up the pharmaceutical trade, the import of pharmaceutical are increasing year by year, but the export is not (Fig. 8). The deficit is expanding every year. Many of the observers are saying this is the proof that Japanese pharmaceuticals are losing its competitiveness, but I don't think so because if you look up the technology trade balance, this is the payment for the patent (Fig. 9). Payment received is much larger than the payment being made. A lot of patent money is coming into Japan from abroad. That indicates perhaps, number one,

Fig. 6　Future direction

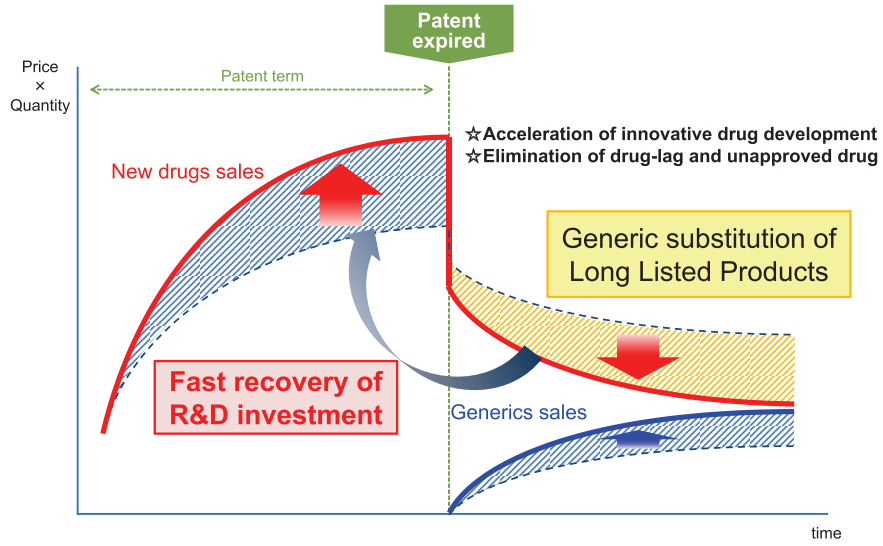


Fig. 7 Changes in the volume share of generic drugs and the target values

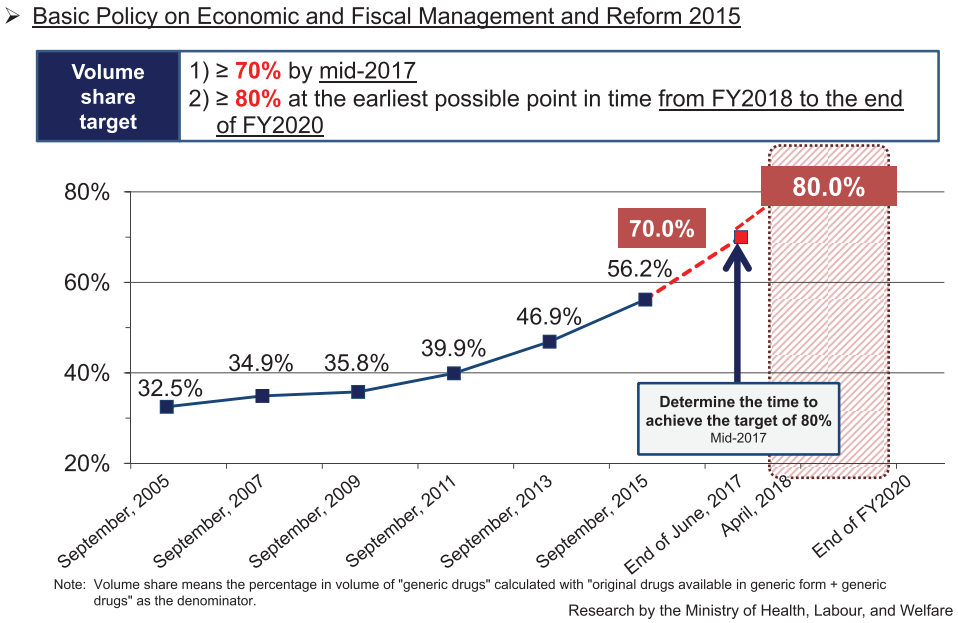
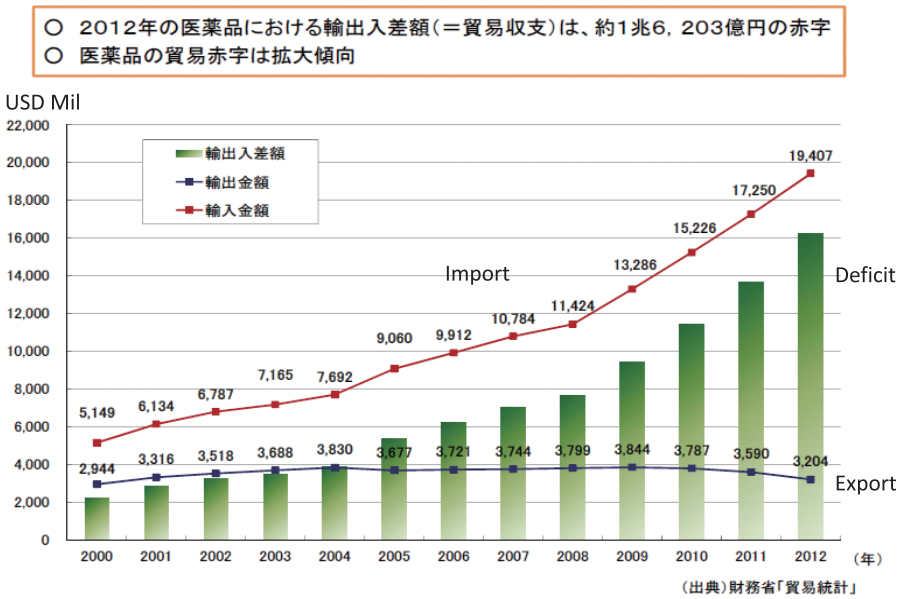


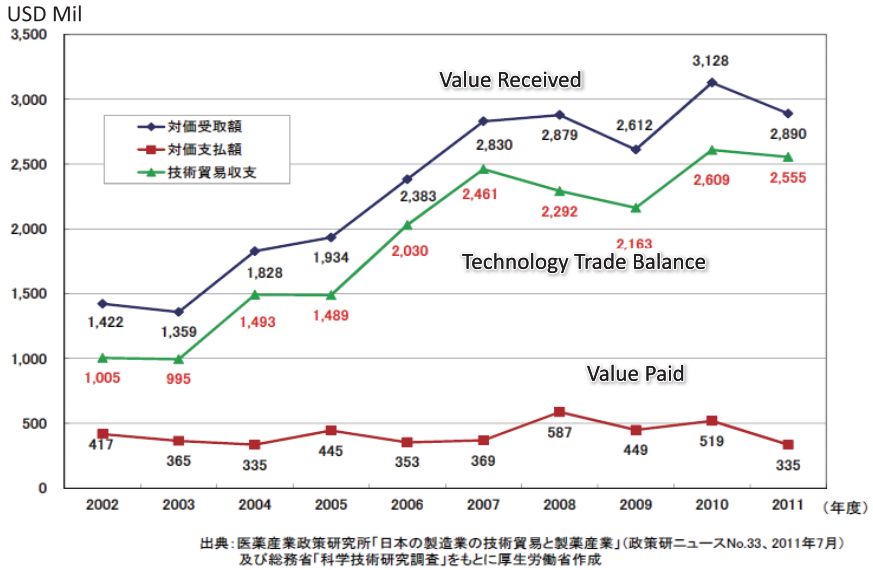
Fig. 8 Pharmaceutical trade



Japan might be strong in basic science and healthcare and they have the patent, and clinical science is perhaps in the U.S. and they are paying the patent to Japan, or the Japanese companies are going into the U.S.. Why? Because the pricing is much favorable in the U.S. than Japan. So, it's inevitable that, first, they go to the U.S. and then come back to Japan with the Japanese products (Fig. 10).

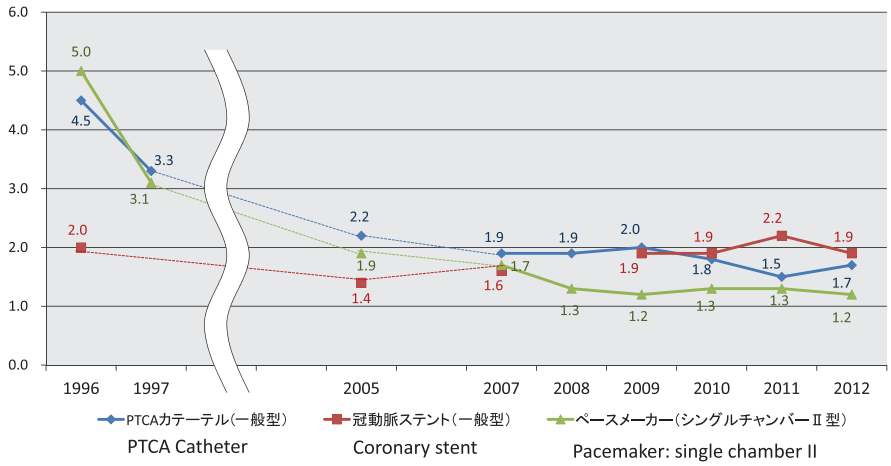
If you compare the corporate tax paid by industries, this is automobile and this is consumer prod-

Fig. 9　Technology trade balance in pharmaceuticals



出典：医薬産業政策研究所「日本の製造業の技術貿易と製薬産業」（政策研ニュースNo.33、2011年7月）
及び総務省「科学技術研究調査」をもとに厚生労働省作成

Fig. 10　Major medical device: price comparison (Japanese reimbursement/overseas average price)



＊Overseas average: US, UK, Germany, France

ucts, electronics, IT, and iron and steel (Fig. 11). We did have the Lehman Shock in 2007. If you see all the other industries except pharmaceuticals, they jump down in corporate tax revenue, but pharmaceuticals are less susceptible to economic trends. Why, because if it's a matter of life and death, price elasticity is very small.

So, Ministry of Health's position about pharmaceutical industry is we regard them as chicken that lays the golden egg. They are less susceptible to economic trends, and we have to compare the tax revenue coming from the industry, or the pricing down and creating resources for fee reshuffling, which is happening every 2 years, and they are very connected to the final exit of clinical trials. We do have the very important instrument such as

Fig. 11 Corporate tax revenue by industries

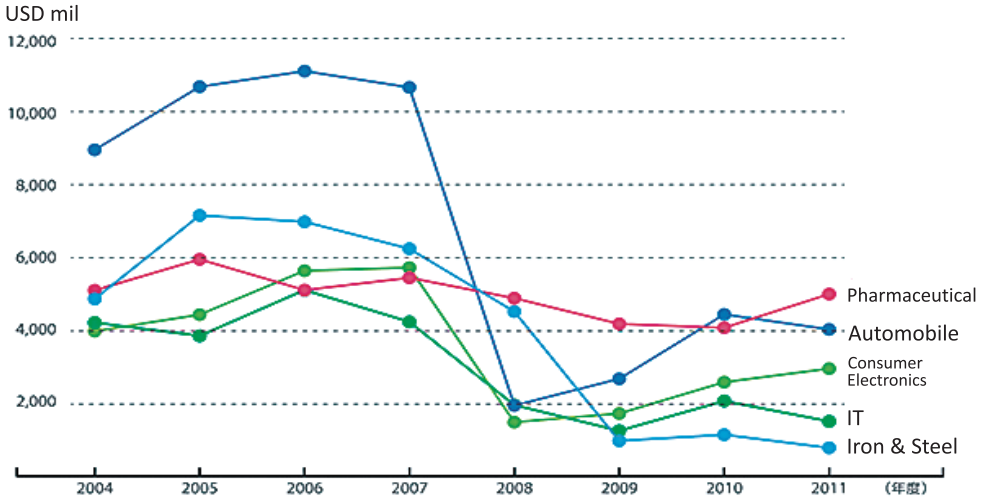
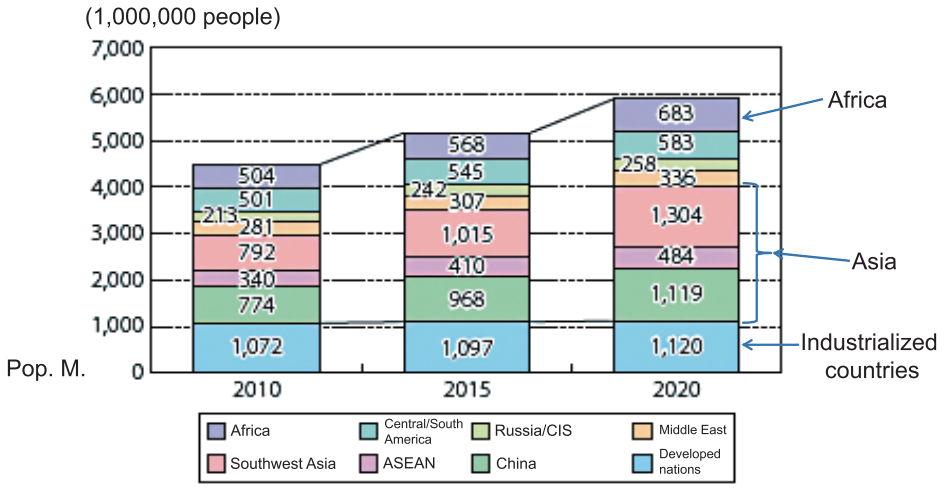


Fig. 12 Regional middle/high income groups



Reference: Household finance population by household disposable income. Calculated by household finance ratio of each income bracket multiplied by population. Household finance ratios for each income bracket in 2015 and 2020 are Euromonitor estimates.
Document: Created from Euromonitor International 2013, UN "World Population Prospects: The 2010 Revision."

approval or pricing, so we can work with the industry. We are trying to shift resources from long listed products to innovative products. If you see the growth of employment by industry, the biomedical/medical device industry in the U.S. is much larger than others. Next, this indicates where the medium or high income group resides (Fig. 12). For 2020, 60% are living in Asia and Japan is about 10% of industrialized countries, so almost 70% of high income or mid-income group is residing in Asia. In addition, we do share similar genetic background. We are Mongoloids. We have advan-

tage in terms of creating the pharmaceutical/medical device market in this part of the region.

5. Trends in medical research

This indicates the comparison between 2001 and 2015 of the world's top 15 pharmaceutical sellers (Table 2). You have only two biological products in 2001 but nine biological products in 2015. But we do have a problem. If you compare the number of pharmaceutical products approved by major countries (U.S., Japan, U.K., Germany, Switzerland, and France), the upper parts are the source and seeds coming from ventures and academia and the lower parts are in-house R&D (Fig. 13). Traditionally for the lower chemical compounds, you have large chemical library in-house and you check and balance between trial and error. This is the big phar-

Table 2　Top 15 items on world sales ranking (2001/2015)

○ Comparing drugs with a higher-level of global sales in 2015 to 2001, recently sales per drug have increased significantly. The proportion of biopharmaceuticals to total sales has also increased.

2001

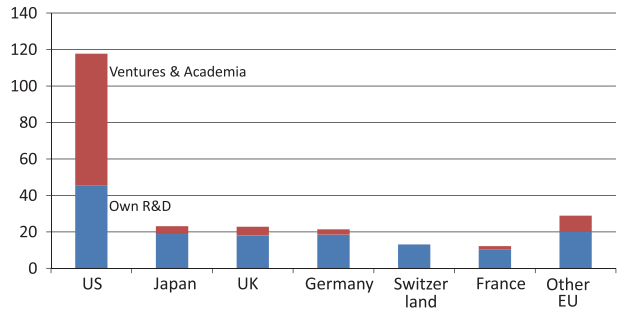
	Brand name	Generic name	Therapeutic category	Manufacturer name	Sales ($ mil.)	Year-on-year
1	Zocor (Lipovas)	Simvastatin	Hyperlipidemia	Merck	6,670	26%
2	Lipitor	Atorvastatin	Hyperlipidemia	Pfizer	6,449	28%
3	Omepral/ Prilosec	Omeprazole	Anti-ulcer PPI	AstraZeneca	5,684	-7%
4	Norvasc	Amlodipine	Antihypertensive Ca blocker	Pfizer	3,582	7%
5	Mevalotin/ Pravachol	Pravastatin	Hyperlipidemia	Sankyo Co./BMS	3,509	5%
6	Procrit/ Eprex	Epoetin Alpha	Renal anemia	J&J	3,430	27%
7	Takepron	Lansoprazole	Anti-ulcer PPI	Takeda/TAP	3,212	25%
8	Claritin-D	Loratadine	Antihistamine	Schering-Plough	3,159	5%
9	Celebrex	Celecoxib	COX-2 inhibitor	Pharmacia	3,114	19%
10	Zyprexa	Olanzapine	Schizophrenia	Eli Lilly	3,087	31%
11	Glucophage	Metformin	Diabetes	Merck KGaA/BMS	2,682	55%
12	Seroxat/ Paxil	Paroxetine	Antidepressant SSRI	GlaxoSmithKline	2,674	16%
13	Vioxx	Rofecoxib	COX-2 inhibitor	Merck	2,555	18%
14	Zoloft	Sertraline	Antidepressant SSRI	Pfizer	2,366	11%
15	Epogen (Espoo)	Epoetin alfa	Renal anemia	Amgen	2,150	10%

2015

	Brand name	Generic name	Therapeutic category	Manufacturer name	Sales ($ mil.)	Year-on-year
1	Sovaldi/ Harvoni	Sofosbuvir/ Ledipasvir	Chronic hepatitis C	Gilead Sciences	19,140	54%
2	Humira	Adalimumab	Rheumatoid arthritis/ Crohn's disease	AbbVie/Eisai	14,357	11%
3	Enbrel	Etanercept	Rheumatoid arthritis/ Crohn's disease	Amgen/Pfizer/ Takeda	9,036	1%
4	Remicade	Infliximab	Rheumatoid arthritis/ Crohn's disease	JJ&J/Merck/ Mitsubishi Tanabe	8,931	-10%
5	Rituxan	Rituximab	Anticancer/ Antirheumatic	Roche/Biogen	8,675	-1%
6	Lantus	Insulin glargine	Diabetes/ Insulin analog	Sanofi	7,090	-11%
7	Avastin	Bevacizumab	Metastatic colon cancer	Roche/ Chugai Pharma.	6,959	9%
8	Herceptin	Trastuzumab	HER2 breast cancer	Roche/ Chugai Pharma.	6,807	10%
9	Januvia/ Glactiv	Sitagliptin/ Combination	Type 2 diabetes/DPP4	Merck/Ono/ Almirall	6,324	0%
10	Prevenar	Pneumococcal vaccine	Vaccine	Pfizer	6,245	40%
11	Revlimid	Lenalidomide	Multiple myeloma	Celgene	5,801	16%
12	Crestor	Rosuvastatin	Hyperlipidemia/ Statin	Shionogi/ AstraZeneca	5,775	-9%
13	Adoair/ Seretide	Salmeterol/ Fluticasone	Anti-asthmatic/ COPD	GSK/Almirall	5,663	-14%
14	Lyrica	Pregabalin	Neuralgia/Epilepsy	Pfizer/Eisai	5,044	-6%
15	Eylea	Aflibercept	Senile macular degeneration	Regeneron/Bayer/ Santen	4,837	47%

* Shaded items are biopharmaceuticals. Underlined items are therapeutic antibodies.
Source: Created by the Office of Pharmaceutical Industry Research, based on "Pharma Future 2002 No. 136" (Uto Brain Co., Ltd.) and "NEW Pharma Future" (June-July issue 2016) (Iyaku Keizaisha) published by KEN Pharma Brain.

Fig. 13　Origin of new chemicals



Source：Robert Kneller, *Nature Reviews Drug Discovery* (November 2010)

maceutical company's model, but for bio-products, it's not like that. You see the enzyme is not working. You see the other mechanisms are working at the bedside, and they are coming universities, academia, and ventures. I would see that the U.S. is accommodating this type of new trends of where the new seeds are coming from.

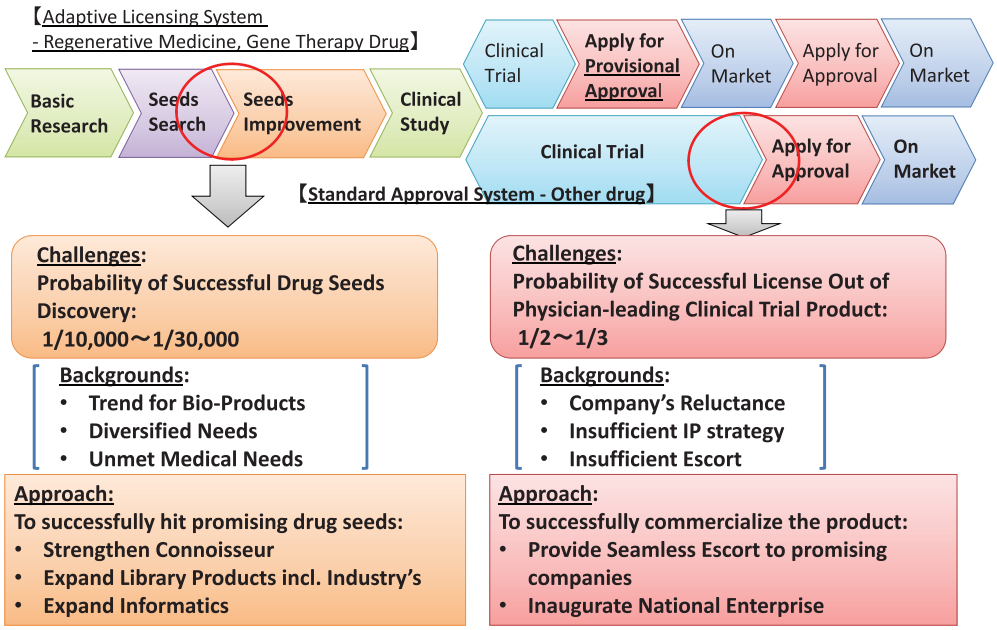
You can see an old chart comparing basic healthcare science and clinical healthcare science. These are the major countries, and this is the major journals in basic research, *Nature*, *Medicine*, *Cell*, and in clinical research, *New England Journal*, *Lancet*, and *JAMA*. Of course, the U.S. is always on top. For Japan, basic research is around third place, but clinical research is 18th place while China is on 15th place. Now China is much larger. For the future direction, our view is how to strike the best balance between promotion of innovation and securing the financial stability of healthcare system, but we do have to ensure transparency and predictability of our pricing and approval system for the industry. We do have to balance between patients' value and quality of care.

6. Future direction of Japan's pharmaceutical research

I want to highlight some of the issues Japan is now trying to do in the process of approval and pricing (Fig. 14). First is early conditional approval. Previously, you had to have both safety assurance and effectiveness assurance then we approve the pharmaceutical. But for the early conditional approval, safety has to be assured, but effectiveness, efficacy can be estimated. Then we have the first-stage approval and going into the market and collect the real-world data after 1〜2 years and then we do the final approval. That is the early conditional approval. We started the early conditional approval for regenerative medicine.

This is what happened in the regenerative medicine products in pipeline, R&D. Before the introduction of the early conditional approval in 2012, the pipeline in Japan is only 4, but for 2017, after

Fig. 14 Optimization of seeds for drug discovery



the introduction of the early conditional approval, it became 15 times larger (In the same period, 88 to 173 in the U.S., 42 to 80 in European Union, 27 to 6 in South Korea). It is not only Japanese regenerative medicine company, but also U.S., North America, and European companies are coming in, because they want to have first-in-the-world approval to make financing much easier. This is what is happening for the cancer drug gefitinib. It was approved first in 2002 for all lung cancers. At that time, the effective rate is around one in four patients and the death related to the drug was around 920 per year. But in 2011, the indication has been changed. It will be prescribed only after testing EGFR, one of the genes mutation, and then the efficacy was about 3 out of 4 and the annual death was limited to 180. That's the victory of genomic information on prescription.

Similarly for lung cancer in 2001, we didn't know any genes connected or causing the lung cancer at the time, 18 years ago (Fig. 15). Now in 2017, we know about three-quarters of lung cancer are being caused by some of the mutations of the genes. In this country, about 60% of these gene mutations have effective pharmaceuticals approved. But I would say there are only 20% pharmaceuticals not approved in this country, or they are off-label use. The question is how we can approve these types of things. The issue is whether there is incentives for pharmaceutical companies to do very expensive clinical trials for this type of indication. For instance, Her2, of course, they do RCT (randomized clinical trial) for breast cancer, but if patient with lung cancers caused by Her2 are very limited, are they going to do the clinical trials? Of course not, because it would be costing millions of dollars for RCT, but the sales would be very limited. What we are going to do is to work with these pharmaceutical companies and do physician-oriented small-size RCT for very limited number of high-grade hospitals and then do very limited number of cases (Fig. 16). If it's effective, then expand the indication. That I would say is the way to expand the indication as early as possible working with the industry.

You can see the world GDP by years graph taken

Fig. 15　Advancement in cancer precision therapy ～ Case of lung cancer ～

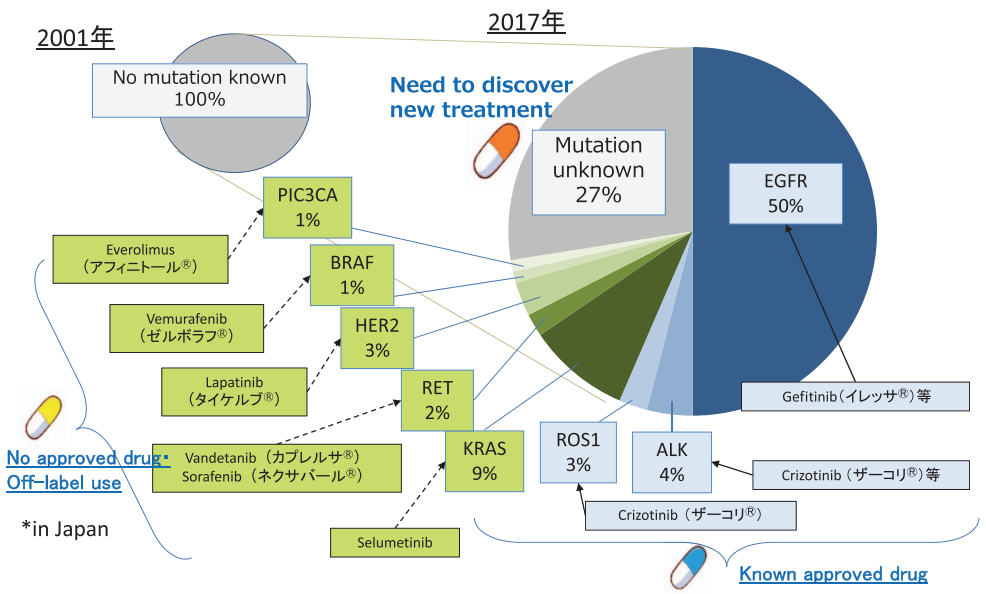
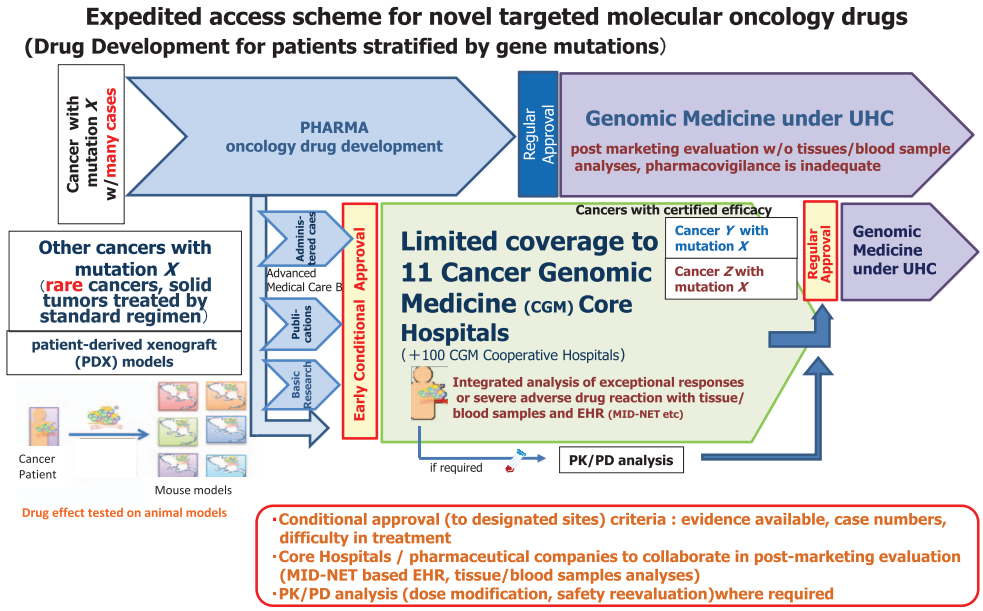


Fig. 16 Conditional approval system with novel pharmacovigilance program



by the journal *Economist*. If you look at 1820, the beginning of 19th century, which countries are occupying world GDP? It's China and India, about 70%. Why, because at that time, GDP is represented by agricultural output. Agricultural output is almost equal to the size of the population. But with the introduction of steam engine and industrial revolution, all the other European countries, Japan, and North America are occupying most of the world's GDP.

Why I am showing this? I would say the same thing is happening about artificial intelligence (AI). If you could introduce AI into healthcare, agriculture, or service industry, then you can become advanced countries for the next century, but if you don't, you are not. An example of AI is the capsule endoscopy. It takes thousands of photographs. If a specialist is checking all the images, it will take 2～3 hours, but if you use AI to screen the doubtful images, the AI can do it in 100th of a second and then the specialist will be checking a few images that might be the disease. Secondly, there was an article in *JAMA*[*2]. This is the mutation of breast cancer, whether the AI or pathologist could judge the mutation correctly. The result showed that AI correctness is about 99% while top 11 U.S. pathologists only 81%. In this case of testing the metastasis of breast cancer, the AI is much more accurate than the pathologists.

7. Ways to make Japan R&D friendly

What we intend to do is early conditional approval; value-based, not cost-based, pricing; single-arm approval and HER (electronic health data)-based, speedy, less costly post-marketing surveillance, because previously pharmaceutical

[*2] Ehteshami Bejnordi B, et al. Diagnostic assessment of deep learning algorithms for detection of lymph node metastases in women with breast cancer. *JAMA*. 2017. 318 (22): 2199-210.

companies were sending people to hospitals and collecting data. It will be costing a lot of energy, time, and money. But if the EHR is connected through internet, you can just push the button and then collect possible side effects that could reduce the investments (Fig. 17).

Lastly, this is about the registry of patients (Fig. 18). We are trying to expand the registry, and currently, it's only being used for the patient recruitment for the RCT. But for future, what we are trying to do is the single-arm trial, because if you have very robust, ample-sized registry, then you know how the disease will progress over time. In that way, you don't have to do the controlled group or RCT. You can just check the intervened group only. That could reduce the size of the target population and the cost of RCT.

My final message is about the horizons in health innovation. The changes in drug discovery and business model are changing from the role of chemical to bioproducts. We have to have the very shortcut and fair evaluation system for approval and pricing. For us, we need to have Japan-based, not Japanese company based, R&D for pharmaceutical and medical devices so that Japanese population could entertain the fruit of innovation as early as possible. We have to recognize that Japanese national mentality is risk-avert and perfectionist. We have to think about immunity for PMDA (Pharmaceuticals and Medical Devices Agency), which is the FDA (U.S. Food and Drug Administration) counterpart, examiner/investigator, because for FDA investigator, they have the immunity unless they are involved in criminal act, but for PMDA, they don't have immunity. They might be sued by misjudgment. That's why they have to be cautious in their investigation. If the approval is delayed in this country, it's not for the "examination lag," because the period for examination is exactly the same as Europe or the U.S., it is the "application lag". We have to introduce a very favorable environment for R&D in pharmaceutical companies and medical devices company so that we could work together to bring in those R&D activities in this country. Thank you for your attention.

Fig. 17　Super hi-way toward sustainable innovation: act of 4

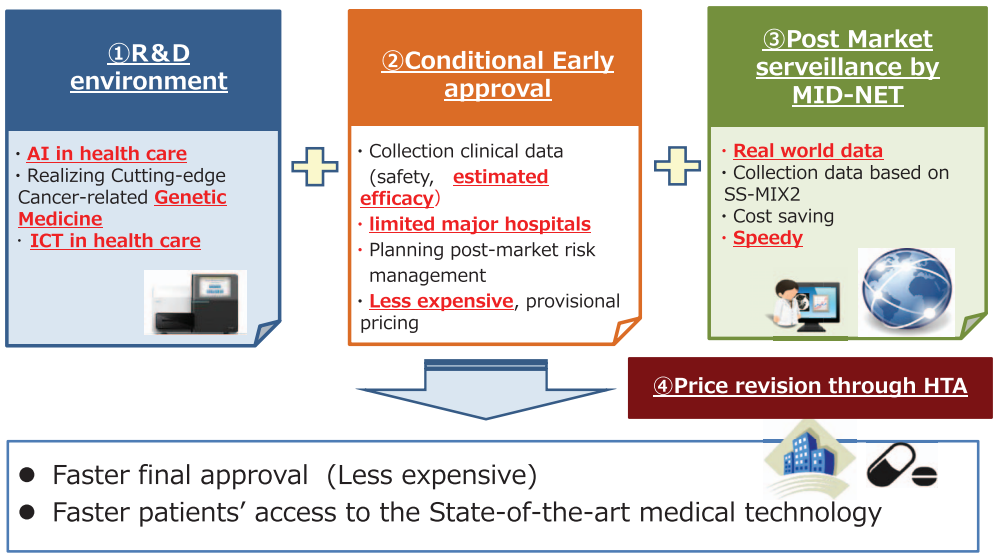
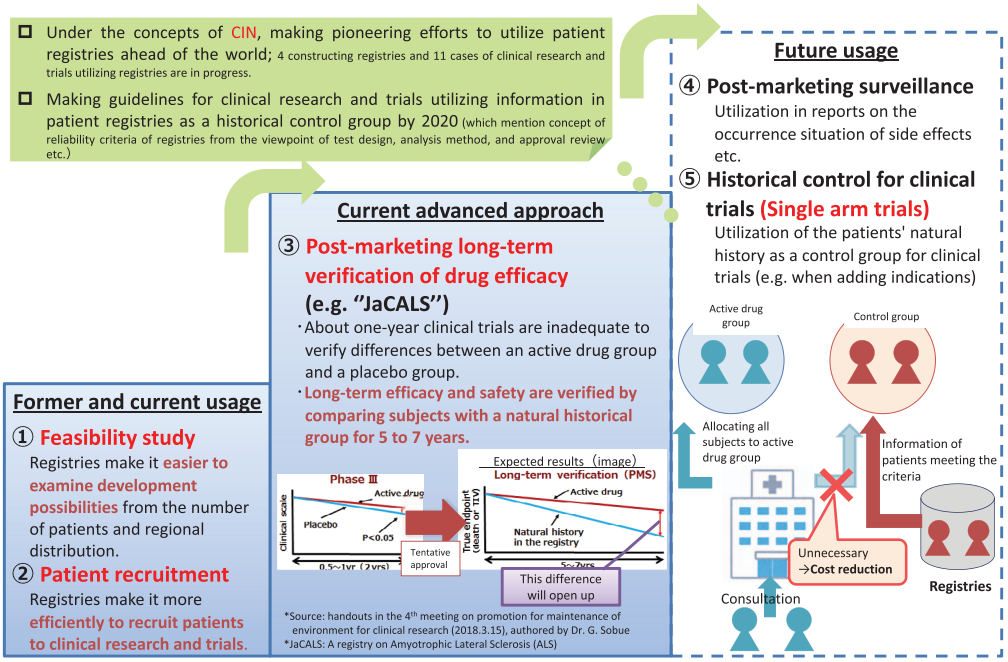


Fig. 18 How to utilize disease registration systems (patient registries)



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