Chapter 5
Science, Technology, and Innovation Policy: Proposal of Preemptive/Precision Medicine Strategy (Including DOHaD)

Masahiro Tsuji

Abstract Prevention is an extremely important part of welfare efforts for humans. I introduce the new concepts of "preemptive medicine" which indicate the direction we should take to realize prevention. As one of the specific R&D strategies toward the realization of prevention, I propose research subjects and a promoting system with a focus on "preemptive medicine/precision medicine (including DOHaD)." Additionally, I propose the measures for promoting the social implementation of technologies for "life-course health care" as a future vision beyond them.

Keywords DOHaD · IoBMT · Life-course health care · Preemptive medicine · Precision medicine · R&D strategy

Abbreviations

DOHaD	Developmental Origins of Health and Disease
IoBMT	Integration of Bio-Medical Things
QALY	Quality-adjusted life year
QOL	Quality of life
R&D	Research and development

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5.1 R&D Concept Based on Social Trends in Japan: "Preemptive/Precision Medicine (Including DOHaD)"

5.1.1 Data on Social Trends in Japan

In Japan, the birthrate is decreasing, and the population is aging more rapidly than anywhere else in the world. The total population is expected to decline considerably in the future, and the decline is forecast to be most remarkable in the "working-age population (population 15 to 64 years old)." It is forecast that a "piggyback-like" society where one aged person (65 years old or older) is supported by about 1.3 "working-age persons." Moreover, soaring medical expenses and care expenditure are expected due to advanced medical technologies and increase in medicine/care needs, etc.

These issues are now becoming more and more serious. If this situation is overlooked, we will face a severe and difficult future plagued with declining economic growth caused by reduced domestic demand, declining domestic production capacity caused by the decreased labor force population, the downfall of the medical/care systems, etc. However, this future outlook can be changed by promoting strategic science and technology policies from the medium- and long-term viewpoint as soon as possible.

5.1.2 Viewpoint of the Formulation of an R&D Strategy (Relation with Social Needs)

On the basis of the data on social trends as shown in Table 5.1, the various issues and social needs in Japan may, I believe, be summarized into the following three points.

1. "People" (e.g., many children grow up healthy. Many aged persons have attained a high QOL.)
2. "Government" (e.g., appropriate medical/care systems responding to soaring medical expenses and care expenditure and medical security)
3. "Academia and industry" (e.g., development of science and technology and health care and medical technology and industry activation).

These are all important social needs. However, some parts of them are inconsistent with each other. For example, the needs of the "people" to use the latest medical technologies (extremely high priced in many cases) are inconsistent with the needs of the "government" to control the rapid increase in medical expenses from the standpoint of sustainability of the national finances.

It will be essential for the future policy of science and technology to satisfy social needs from these three points of view "in a well-balanced and simultaneous manner." With a view of realizing such a goal, I have been involved in the collection of information as seen from a bird's-eye view (trends in R&D, science and technology policies, and industries) and discuss R&D strategies with researchers and

Table 5.1 Data of Japan's social trends

	Past	2010	Future forecast
Total population	93 million people (1960)	128 million people (2010)	87 million people (2060)
Working-age population (15–64 years old)	60 million people (1960)	82 million people (2010)	44 million people (2060)
Aging rate (share of the aged population (65 years old or older))	5.7% (1960)	23.0% (2010)	39.9% (2060)
Working-age population supporting an aged person	11 persons (1960)	2.8 persons (2010)	1.3 persons (2060)
Medical expenses	31 trillion yen (2000)	37.8 trillion yen (2010)	54 trillion yen (2025)
Care expenditure	3.6 trillion yen (2000)	8.4 trillion yen (2010)	19.8 trillion yen (2025)
Import surplus (pharmaceuticals)	0.6 billion (2000)	1.9 trillion yen (2014)	–

(Reference: website of the Cabinet Office, the Ministry of Health, Labour and Welfare etc.) [1]

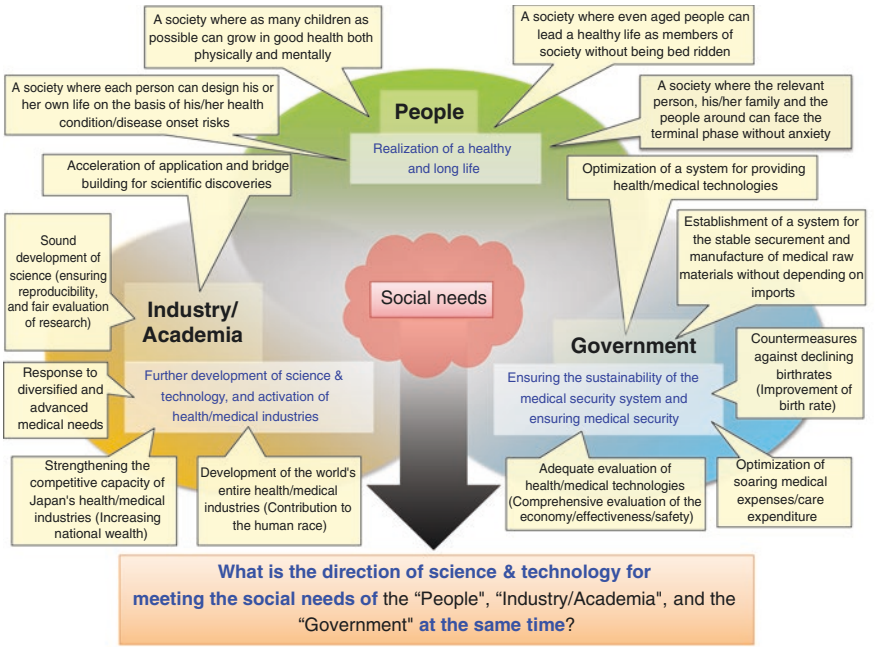

Fig. 5.1 Points of view required for the formulation of R&D strategies Japan ought to pursue (personal views)

policy-making authorities and group workshop. In addition, I support the formulation of specific R&D strategies as well as the initiation of national projects based on the strategies (Fig. 5.1).

5.1.3 New Concepts of Science and Technology: "Preemptive Medicine" and "Precision Medicine"

Diseases expected to decrease the QOL of people and impose a considerable burden on society in the future include cardio-metabolic diseases, chronic obstructive pulmonary disease (COPD), mental disease, dementia, cancer, etc. It is a serious challenge not only for Japan but also for the entire world on how to address these diseases [2].

These diseases are caused by the interaction between genetic predisposition and environmental factors (lifestyles (meals, physical exercise, etc.)) in the long term, coupled with disease risk factors that gradually accumulate and lead to a disease onset. It is not easy to provide curative treatment after the disease onset, and a higher improving effect may be obtained through intervention at an earlier stage. For this reason, in 2010, I proposed a concept of comprehensive disease prevention called "preemptive medicine" [3]. The concept of "preemptive medicine" aims to maintain the health of the people by making use of highly cost-effective intervention technologies (lifestyles (meals, physical exercise, etc.), pharmaceuticals, and so on) and to prevent the disease onset and advancement in severity after identifying high risks by low-cost and highly accurate disease onset prediction technologies (genetic predisposition, biomarker, clinical information, social data, etc.). In 2014 we proposed a concept that added the concept of DOHaD to "preemptive medicine."

Meanwhile, I am now making an in-depth study on the "Precision Medicine Initiative (US)" and re-defining "preemptive medicine (including DOHaD)" in a constructive manner. "Precision medicine (in Japan)" positions, in addition to disease onset prevention, focused on by "preemptive medicine," "prevention of advancement in severity," and "prevention of paroxysm and recurrence" as important targets for disease prevention. And in these three phases of disease prevention, people are stratified and individualized on an appropriate scale from the viewpoints of economy, safety, and effectiveness. In addition, in R&D activities for this purpose, the direction of research should be focused on "IoBMT (Integration of Bio-Medical Things, the new research and development concept we defined)," driven by the collection of high-quality data and big data analyses (including artificial intelligence).

The concept of "preemptive/precision medicine" allows for not only the enhancement of people's QOL but also the activation of industries and the optimization of medical expenses/care expenditure, simultaneously satisfying social needs, as shown in Fig. 5.2.

5.1.4 Materialization of the Concept of "Preemptive/Precision Medicine"

Both a technology to "forecast" the onset/advancement in severity/paroxysm and recurrence of a disease and a technology to "intervention" in curative measures are needed to realize "preemptive/precision medicine." The overview of these technologies is as follows:

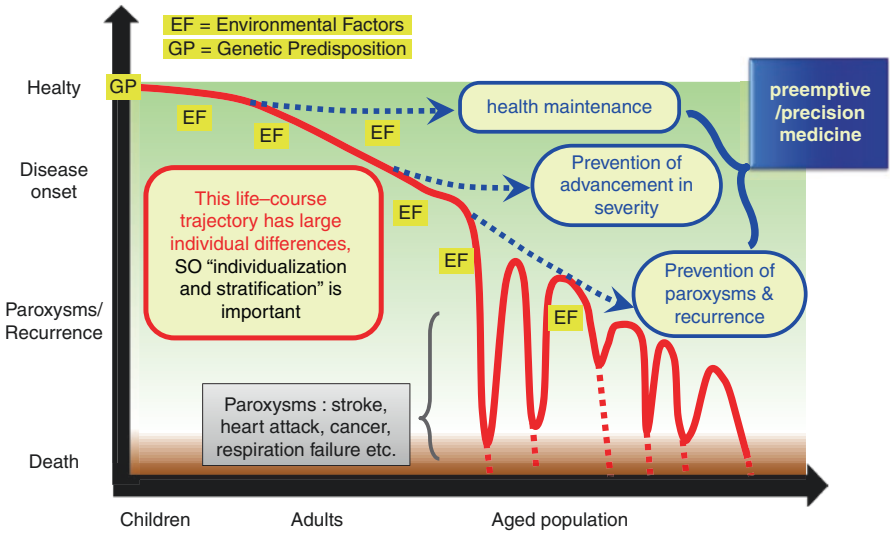

Fig. 5.2 A new concept of disease prevention, "preemptive/precision medicine". This is a new concept of disease prevention based on the principle of "medical science for individuals," which stratifies/individualizes high-risk diseases and forecasts the disease onset, advancement in severity, paroxysms, and recurrence with a high probability through the use of genetic predisposition, biomarker, clinical information, social data, etc., in addition to establishing appropriate preventive intervention (improvement of lifestyles (meals, physical exercise, etc.), pharmaceuticals, etc.) according to the risks

First, depending on the type of each disease, the process leading to the onset/advancement in severity/paroxysm and recurrence of the disease differs. Therefore, it needs to be identified what type of how intense risk factors exist at which period of a person's life in an exhaustive manner (e.g., genetic predisposition, biomarker, clinical data, social data, etc.). Then it is necessary to analyze those factors in chronological order, establish high-precision "forecasting" technology, and stratify/individualize the persons on an appropriate scale from the viewpoints of economy, safety, and effectiveness. And finally, by establishing highly cost-effective intervention technology (for lifestyles (meals, physical exercise, etc.), pharmaceuticals and so on) according to the "forecast" result of each disease, prevention of the onset/advancement in severity/paroxysm and recurrence of the disease.

In order to establish these technologies, strategic R&D integrating various fields concerning life science and medical science is required. In recent years, important scientific insights likely to be a key to realizing "preemptive/precision medicine" have been noted one after another. In this document, while paying attention to the viewpoint of "DOHaD" as one of those insights, I describe the unified strategy for realizing "preemptive/precision medicine."

5.1.5 Overview of DOHaD

In realizing "preemptive/precision medicine" [4, 5], DOHaD (Developmental Origins of Health and Disease) [6] gives an important indication. DOHaD is a significant insight found through the research on birth cohorts, etc., conducted over the past few

decades in Europe. DOHaD has shown in many instances the correlation of environmental factors (nutritional status, etc.) during the period from the fetal stage to infancy with obesity in childhood and at later stages, cardio-metabolic diseases (diabetes, cardiovascular disease, etc.), developmental disorder, mental disease, etc. These diseases are projected to become more and more serious issues for the entire human race in the future, and R&D focused on DOHaD will be very important in the future.

In the past, preventive measures against obesity and cardio-metabolic diseases in Japan were mainly targeted at middle-aged and elderly people who looked healthy. On the other hand, DOHaD has indicated the importance of appropriate care from the fetal stage to infancy. Moreover, going back further than the fertilization stage, the environments and health conditions of parents in their puberty (e.g., obesity, etc.) may be important, too. Other issues also exist, such as the lack of measurement/diagnosis technologies, the difficulty of intervention experiments, etc. However, in future research on disease prevention, it will be significant to incorporate the viewpoint of DOHaD.

5.1.6 Significance of Implementing DOHaD Research in Japan

Representative risk factors found through the cohort analyses in Europe include undernutrition of pregnant women, low birth weight of babies, age of women when they give birth, etc. Compared with those in other developed countries, Japanese women have a high proportion of thinness (suggestive of undernutrition) [7]. Also influenced by the concept of "have a small baby and raise it to grow big" peculiar to perinatal care in Japan, the proportion of low birth weight babies is high [8]. Additionally, in association with women's activated participation in the society, the average age of marriage has increased coupled with childbearing age. These facts show the possibility that babies in Japan have a high risk of disease from birth. Thus, there is an urgent need for strategic R&D focused on DOHaD in this country.

The presence of ethnic differences also needs to be noted. DOHaD research is led by European countries, but European countries differ from Japan in the genetic predisposition of people, environmental factors, medical systems, etc. Therefore, insights obtained in the European region cannot be applied as they are to Japanese people. In fact, their life span, body shapes, disease patterns, etc. are considerably different. For this reason, we need to immediately build up scientific evidence targeting Japanese people.

5.2 R&D Strategy for "Preemptive/Precision Medicine (Including DOHaD)"

First, we should establish epidemiological research bases (cohort, data of the administration, etc.), and we should pursue the collection, management, and utilization of data. Considering the continuity with the data collected in the past and the latest

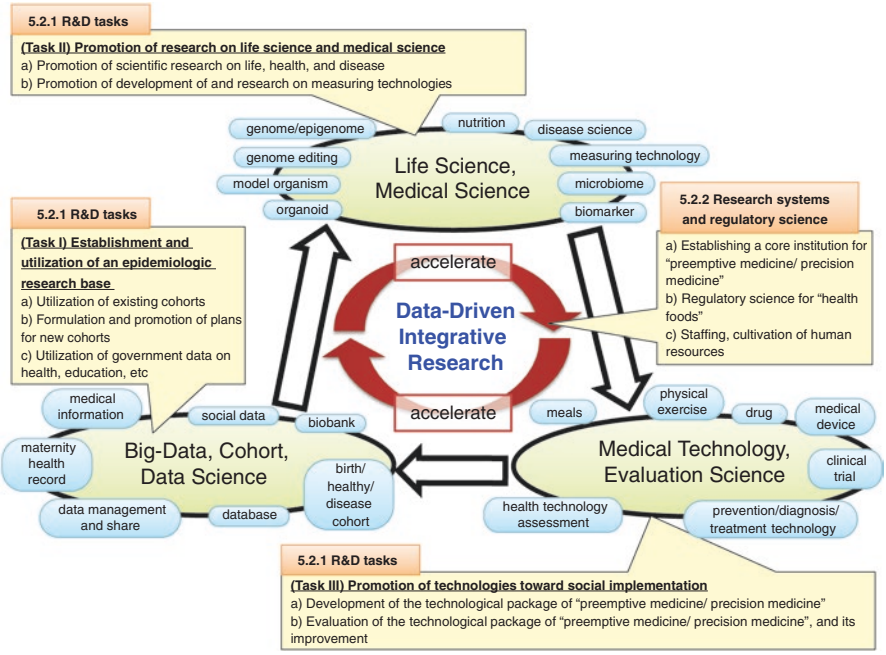

Fig. 5.3 An overall image of R&D subjects

knowledge, etc., we should specify important items for collection and collect data from a long-term point of view in a flexible manner. Hypothesis found in the epidemiology research base will lead to the clarification of detailed mechanisms through life science and medical science research, and new hypothesis found during the process should be verified on the basis of the epidemiology research base. By accelerating these cycles, a lot of scientific knowledge will be obtained, and development of the technological package of "preemptive/precision medicine" will progress significantly. In parallel with these, we will need to promote evaluation and research activities on the impacts on the economy, society, and people's health. Then, on the basis of the evaluation results, an optimal technological package should be established. We will identify new hypothesis from the data obtained through their use by many people in society and further promote life science and medical science research. It is an important issue to accelerate these data-driven researches, "IoBMT (Integration of Bio-Medical Things)."

The main direction of research on "preemptive/precision medicine" is as stated above. The main subject of this document, i.e., DOHaD, is one of the important approaches to research on "preemptive/precision medicine." I will describe specific R&D subjects, research systems, and regulatory science that should be pursued in Japan in the future (Fig. 5.3).

5.2.1 R&D Tasks that Should Be Established in Japan ("Preemptive/Precision Medicine (Including DOHaD)")

(Task I) Establishment and utilization of an epidemiologic research base: Collection and sharing of high-quality data

(a) **Utilization of existing cohorts.**

Existing cohorts (birth cohort, healthy person cohort, disease cohort, etc.) have been built up and maintained through many years of work by many researchers and participants, and this knowledge should be made the most of.

From the viewpoint of DOHaD, a lot of insights are expected of an integrated analysis on the information obtained from existing birth cohorts.

Specific Research Subjects

- Establishment of a system for integratively managing the data and biological samples collected from existing cohorts with high accessibility for researchers [compilation of a database, biobanking].
- Flexible introduction of the latest science and technology and insights in existing cohorts and collection of data (environmental and lifestyle data, personal device, and sensor data) and biological samples (medical records, genome, metabolome, microbiome, etc.) with higher values on the basis of the sufficient agreement of the participants.
- Collection of various social data (family environment, parent-child relationship, occupation, annual income, mental stress, etc.) on the basis of the sufficient agreement of the participants.

(b) **Formulation and promotion of plans for new cohorts.**

If some important data items or biological samples exist that are hard to obtain from existing cohorts, new cohorts shall be established on the basis of sufficient discussions and careful planning.

From the viewpoint of DOHaD, birth cohort and prenatal cohort (from pregnant women, etc.) are expected to be established. However, as such efforts will incur a huge cost, careful preparation is required (Refer to *[Column 1]*).

Specific Research Subjects

- Implementation of experimental efforts concerning small-scale cohorts (e.g., introduction of wearable devices) and practical efforts for larger cohorts to be extracted.
- Promotion of cohort research targeting events expected to result in a lot of small-scale benefits (pregnancy diabetes, natural pregnancy cases/pregnancy cases supported by assisted reproductive technology, etc.) and analytical research on the data thus obtained.
- Formulation and implementation of large-scale and long-term birth cohort plans (→It is required to have detailed discussions on various expert groups

(epidemiology, life science, medical science, economics, sociology, ethics, pedagogy, etc.) as well as detailed plans on data collection items, promotion system, procurement of long-term operating funds, etc.)

(c) **Utilization of government data on health, education, etc. (including maternity health record books, etc.)**

In Japan, a huge amount of data already exists on health/education, etc., collected by administrative organs. Although there are issues concerning the difference in competent administrative entities and insufficient standardization of data items, etc., the data is still a mountain of treasure and should be made the most of.

From the viewpoint of DOHaD, a lot of knowledge is expected to be obtained through integrated analysis on the data from "maternity health record books," with a history of more than half a century and clinical information.

Specific Research Subjects

- Conversion of various data collected by administrative organs for health/education, etc., into a structured data that allows for integrated AI analysis (curation, standardization, etc.), and compilation of a database on maternity health record books, babies and infants, medical checkup for school children, and medical checkup/measurement of physical fitness/achievement test, electronic chart, statement of medical expenses, medical information, etc., during compulsory education, etc.
- Unification of various data at the national and local authority levels (annual income, family structure, demographic statistics, etc.), compilation of a database, and establishment of a system for appropriately sharing the data.
- Integrated analysis on the data obtained from existing various cohorts and the data from "maternity health record books".
- Acceleration of the digitalization of maternity health record books (It will be an interface for the social implementation of not only data collection methods but also the results of research on DOHaD.)

[Column 1] Studies toward the maintenance and development of longer-term cohorts, biobank, and database

By maintaining cohorts, biobanks, and databases for a long time, over 30–50 years, as the research base and keeping on developing them, their scientific and industrial significance will increase.

As cohorts, biobanks, and databases require a huge amount of labor, time, and cost for establishment and maintenance, a detailed promotion plan is essential. First, we will need to closely survey related trends in and out of the country and hold discussions among all stakeholders of Japan's industrial, academic, and governmental organizations, etc., for 3–5 years. Then, in consideration of the forecast of related technological fields and social needs, etc., in a comprehensive manner, a promotion plan will need to be formulated from a long-term point of view. Experts having strong leadership to put the plan into practice are needed to supervise all the activities and start the implementation phase at an optimal time.

For example, it is expected that the latest scientific knowledge in respect of data collection items and collection methods (wearable devices, innovative analytical technologies, new candidates for disease markers, etc.) will be reflected in cohorts. At the same time, in order to maintain the follow-up rate of cohorts, we need to develop a trusting relationship with cooperating people in respect of cohorts (active communication, appropriate information transmission, etc.). In addition, we should also pay attention to the trend of the individual medical number system scheduled to be introduced in 2020, the electronic health record, etc., which is expected to come into existence sooner or later. Moreover, it is also essential to respond to major changes in these infrastructures for science and technology and medical treatment and to correct the plan flexibly while maintaining the compatibility with collected data.

These efforts require government investment at their incipient stage, but it is unrealistic in the environment of an increasingly tightened national budget to depend only on national funds for a long time. Operating the systems with various financial sources will not only increase their robustness as infrastructures but also make the cohorts, biobanks, and databases worthy of being relied on by various sectors in and out of the country. One of the conceivable directions will be for the would-be beneficiary companies (pharmaceutical, food, insurance companies), organizations (health insurance associations), the government (not a single ministry or agency but multiple ministries, agencies, or government organizations), etc., to bear the operating cost under the condition that they provide knowledge and information thus acquired. We should also immediately start discussions on these frameworks for securing medium- to long-term budgets.

Meanwhile, new trends are emerging, too. For example, a US insurance company (Kaiser Permanente) is proceeding with the compilation of a database and biobank of various information about insured people, while a US genome analysis company (23andMe) is proceeding with the establishment of a large-scale database focused on the genome information of its hundreds of thousands of customers. At present, the scale of the activities of private companies corresponding to these is still small in Japan, but it is expected to significantly expand in the future. While adequately grasping these trends in the private sector, we should discuss and implement the desirable division of roles and linkage in relation to the bases built up by the government.

The above efforts will be an asset to Japan in the future. And further, they will be the source of competition in R&D and will be the backbone of evidence for policy-making.

(Task II) Promotion of research on life science and medical science: Deepening the understanding of life

(a) **Promotion of scientific research on life, health, and disease.**

In order to use the results of research on “preemptive/precision medicine” for commercialization, it is desirable to pursue research on humans. However, it takes a long time for a seemingly healthy person to show signs of a disease or have a paroxysm. Therefore, in actual cases, research using biological samples of model animals or humans (in DOHaD, placenta, umbilical cord blood, the body fluid of pregnant women and babies/infants (blood, urine), etc.) will need to be promoted.

Then, by carrying out an integrated analysis on the knowledge obtained this way with the data acquired from the abovementioned epidemiology base, the knowledge is refined to a highly extrapolated one for humans.

From the viewpoint of DOHaD, the following are two particularly notable topics. One is that it is noted from research on model animals that an epigenome is inherited across generations. This is an important finding which indicates the need to go back further than the fetal stage (to a period before pregnancy, puberty, etc., of the parent) of the relevant person in order to provide adequate preventive measures against a disease. It is expected that more intellectual bases will be built up in the future. The other is that a relationship between microbiome (intestinal flora, etc.) and the child is indicated, in relation to which the Bill & Melinda Gates Foundation has initiated a global effort to start the long-term follow-up of cohorts, etc. Research on microbiomes has also been activated in Japan, and further activation of research on microbiomes targeting the period from fetal stage to infancy is expected [9].

Specific Research Subjects

(1) Development of experimental methods.

- Development and sustainment of model animals making the most of genome-editing technologies (CRISPR/Cas9), etc.
- Development of simulation technologies (simulation of organs/fetuses, the process from birth to aging, inheritance to the next generation (of epigenomes, etc.), the process of evolution of model animals and humans, etc.)
- Use of organism species having peculiar physiology as experimental animals (killifish (short lived), naked mole rat (showing no symptoms of aging), etc.)
- Development of human *in vitro* experiment systems (organoids originating from human cells, organ-on-a-chip, etc.)

(2) Promotion of research on epigenome/genome.

- Elucidation of the mechanism of intergenerational transmission of epigenome (from parents, grandparents, great grandparents, etc.)
- Elucidation of the mechanism of change in epigenomes caused by environmental factors influencing birth and aging and association with phenotypes.
- Elucidation of the relationship between the change in epigenomes during the fetal stage, infancy, and the subsequent process of growth and the disease onset mechanism; exploration of biomarkers/intervention methods.
- Promotion of research on genomes (identification of epigenome-related genes, genes having disease onset risks, etc.)

(3) Promotion of research on nutrition science.

- Identification of the nutrients involved in the change in epigenomes and elucidation of both the physiological significance and the metabolic mechanism.
- Elucidation of the relationship between the profile of microbiomes (intestinal flora), nutrition, metabolism, and exploration of improvement methods.

- Exploration of biomarkers/intervention methods, including the working mechanism of disease nutrients believed to be associated with the onset of diseases and related molecules.
- Elucidation of the influence of excess or deficiency in energy and nutrients, etc. (protein, amino acid, iron, folic acid, etc.), during the period from the fetal stage to infancy on the development/growth and the health condition after maturity, as well as elucidation of the working mechanism and exploration of biomarkers/intervention methods, including involved molecules.
- Establishment of a simple and accurate method of collecting and analyzing data on meals (collection of and analysis on data taken with a smartphone camera and so on).

(4) Promotion of scientific research on diseases.

- Exploration of candidates for biomarkers/treatment technologies on the basis of a disease onset mechanism.
- Acceleration of research on the period from the fetal stage to baby/infant stages by making the most of a host of scientific knowledge accumulated through past scientific research on diseases (onset mechanisms, biomarkers, etc.) (e.g., comparative study on diseases showing similar pathology in babies and infants).

(b) **Promotion of development of and research on measuring technologies.**

The driving force of technology development for "preemptive/precision medicine" is high-quality big data, and measurement technologies for data collection are placed at an important position. It is believed that there are two environments for data collection, i.e., daily data collection using wearable devices and data analysis during medical checkup/examination using precision measuring technologies, each of which requires R&D.

Additionally, from the viewpoint of DOHaD, measuring technologies for fetuses (babies and infants) is likely to be the largest bottleneck. First, since the technologies that can be used to measure the state of fetuses are limited, data on fetuses is especially deficient. In order to realize the improvement of the intrauterine environment on the basis of scientific evidence, a breakthrough is required for measuring and analyzing technologies. When compared with the cases of adults, measurement and analysis of babies and infants involve many challenges, and a more minimally invasive (noninvasive), rapid, and simple measuring method is essential. As both noninvasiveness and ease in measurement are strongly required for the measuring technologies for fetuses, babies, and infants, the established technologies are expected to be developed and applied not only to fetuses, babies, and infants but also to adults, the aged population, etc.

Specific Research Subjects

(1) Development of ultrahigh-precision measurement/analytical technologies and daily data collection/analytical technologies.

- Measurement/analytical technologies for infinitesimal body fluid (blood, urine, saliva, etc.)

- Development of wearable devices (development of sensing technologies, data processing/communication technologies, and data analysis technologies).

(2) Development of measurement/analysis technologies for the state of fetuses.

- Promotion of research on the improvement/sophistication of electrocardiogram for fetuses, implementation of programs for the dissemination of related technologies.
- Development of measurement/analysis technologies for the various parameters of fetuses (blood pressure and pulse wave of fetuses, measurement/evaluation of the growth state in the womb, etc.)
- Development of measurement/analysis technologies for substances contained in maternal blood originating from fetuses (DNA, mRNA, epigenome, protein, lipid, sugar chain, microRNA, etc.)

(3) Development of measurement/diagnosis technologies for the state of babies and infants.

- Development of measurement/diagnosis technologies and minimally invasive (noninvasive), rapid, and simple sampling (painless blood sampling, oral cells, secreted sebum, hair root, and others).
- Development of quantitative evaluation technologies for the state of development and growth.
- Development of innovative measurement/diagnosis technologies (e.g., developmental disorder (autism spectrum disorder, etc.))

(Task III) Promotion of technologies toward social implementation: Sophistication of technologies and dissemination/wider use of them across society

(a) **Development of the technological package of "preemptive/precision medicine" (evaluation/intervention technologies for disease risk).**

By analyzing the big data acquired through the efforts of the abovementioned "Task I", "Task II" and the latest scientific knowledge in an integrated manner and verifying/sophisticating the technologies thus developed, evaluation/intervention technologies for disease onset risk essential for the social implementation of "preemptive/precision medicine" technologies shall be established.

In general, the contribution of each disease risk factor to the onset of a disease is low. In order to enhance the precision of evaluation/intervention models for disease onset risks, it will be effective to carry out analyses focused on multiple disease risk factors and their time series variation. On the other hand, the only approach of Fisher statistics under the assumption of a huge parent population in conventional large-scale randomized trials, etc., by itself has limitations. It is expected that after recognizing a certain degree of uncertainty by making the most of the approach of Bayesian statistics, the number of analyzed cases will gradually be increased and a higher precision evaluation/intervention model for disease onset risks will be established.

Artificial intelligence technology can be noted as a remarkable trend in recent years. At present, efforts aiming to formulate diagnosis/treatment plans using

Watson (of IBM) having advanced machine learning and reasoning functions have been initiated and led by the USA. Additionally, deep learning technologies are attracting a great deal of attention throughout the world. These artificial intelligence technologies have a potential to dramatically accelerate both the development of the technological package of "preemptive/precision medicine" and its social implementation. These artificial intelligence technologies, however, should be appropriately introduced and utilized after identifying the potential of such technologies.

From the viewpoint of DOHaD, the improvement of the intrauterine environment through nutritional improvement, etc., for pregnant women, I believe, will be effective for them (fetuses) as a specific intervention method. In the period of babies/infants and subsequent stages, it will be possible to adopt less invasive methods (improvement of eating lifestyles (meals, physical exercise, etc.)) for smaller onset risks and rather invasive methods for larger disease onset risks (intake of specified nutrients or adequate administration of pharmaceuticals).

Specific Research Subjects

(1) Data groups, etc., required for analyses.

- Extraction of correlation and rules, estimation of the relation between causes and effects, analytical research on major factors, etc., should be conducted for the large-scale time series data groups concerning the health maintenance/disease risk factors acquired from the abovementioned "Task I.": the data groups are as follows:
  - Biological data. Genome information, biochemistry information (protein, metabolites, etc.), vital information (blood pressure, etc.), image information (MRI, etc.) markers, etc.
  - Life data. Meals, physical exercise, life rhythm, the situation of exposure to environmental chemicals, etc.
  - Governmental data groups on health and education, etc. Annual income, family structure, occupation, data on maternity health record books, data on medical checkups for school children/babies and infants, medical checkup/measurement of physical fitness/achievement test during compulsory education, etc., medical checkup data of companies, electronic charts, statement of medical expenses, etc.
- A wide variety of scientific knowledge on health maintenance/disease risk factors acquired by abovementioned "Task II."
  - Knowledge on various vital phenomena: epigenome, nutrition science, behavioral science, biogenesis science, aging science, metabolic science, homeostatic mechanism, microbiome (intestinal flora, etc.)

(2) Development of the technological package of "preemptive/precision medicine" (evaluation/intervention technologies for disease onset risks).

- Analyses incorporating the concept of time series on multiple disease risk factors, sophistication of prevention/diagnosis/treatment technology seeds.

  - Development of integrated analytical technologies for multilayered and multidimensional information.
  - Development of an optimal designing method for clinical research/tests (through the use of Bayesian statistics, etc.)
  - Development and implementation of new bioinformatics technology including artificial intelligence (deep learning technology, etc.)

- Optimal stratification of target groups according to health condition and disease type and establishment of preventive intervention technologies (including the unification of evaluation/diagnosis technologies and intervention technologies).

  - Stratification technologies: Health condition evaluation markers, onset forecasting markers, diagnostic equipment.
  - Preventive intervention technologies: Chemical compounds for improving health condition, pharmaceuticals, new drug modalities (fecal microbiota transplantation, microbial cocktail technology, etc.), digital theraphy (smart phone app), medical equipment, etc.

(b) **Evaluation of the technological package of "preemptive/precision medicine" (health, economic, and social impacts) and its improvement.**

In order to realize a better society through the implementation of technologies, health, economic, and social impacts of the technological package of "preemptive/precision medicine" (mentioned in "Task III-a") need to be evaluated.

In general, short-term and direct effects of disease prevention are hard to see. In particular, as DOHaD takes a long time until the disease onset, this tendency is remarkable in this case. Therefore, efforts to quantitatively visualize the health, economic, and social impacts as much as possible through the prevention of those diseases are extremely important in respect of the following two points.

1. It can be verified in advance how significant the relevant technology is in the medium- to long-term from the viewpoint of people's health/national finances/industries.
2. Development of motivation and change of actions can be expected when the technological impacts are conveyed to the stakeholders of the people, researchers, administrative officers, health-care providers, etc., in an understandable manner.

Specific Research Subjects

(1) Establishment of technologies for evaluating health, economic, and social impacts.

- Refinement of methods for evaluating medical technologies currently used for calculating the standard prices for new medicines.

  - More efficient analyses on a large amount of data and research on modeling as a method that can complement deficient data for analyses (e.g., decision tree model, Markov model, Monte Carlo simulation, etc.)

  - Research for evaluating the health outcome of medical technologies (e.g., cost-benefit analysis (willingness to pay, social cost, etc.), cost-utility analysis (e.g., QALY (product of QOL and years of life), patient-reported outcome).
  - Research evaluating clinical economy (e.g., cost minimization analysis, cost-effectiveness analysis, cost-benefit analysis, cost-utility analysis, cost-of-illness analysis, cost-consequence analysis, etc.)

- Development of a method for evaluating the "preemptive/precision medicine technology," which can be thought of as far more complicated than the calculation of standard prices for medicines: examples of components that need additional analyses.

  - Life expectancy and QOL that can be improved by disease prevention (including the change in QOL and time cost of not only the relevant person but also his/her family members, etc.)
  - Influences on medical expenses and care expenditure (implementation cost of the "preemptive/precision medicine" technology, medical expenses involved in diseases that can be controlled by disease prevention, and those expected to occur in the future).
  - Social cost (loss of opportunities for the work of the relevant persons, social activities, cultivation of the young, etc.)
  - Sense of values of the people (social agreement status, etc., of health/medical care, bioethics, etc.)

(2) Evaluation (health, economic, and social impacts) and improvement of the package of "preemptive/precision medicine".

- Carry out evaluation from the development stage of the technological package of "preemptive/precision medicine" and accelerate the development, correct the direction of technologies, or stop the development. The evaluation method is immature under the circumstances, but by continuing the evaluation in actual fields, the evaluation method can be expected to be established early.

[Column 2] Expectations for pharmaceutical companies

Pharmaceuticals, food (nutrients), etc., are positioned as specific important intervention technologies for "preemptive/precision medicine." In developing these technologies, we set high expectations for pharmaceutical companies.

At present, pharmaceutical companies are mainly engaged in activities for developing diagnostic methods and treatment methods. However, drug development faces many difficulties such as the lack of promising drug discovery targets, a decline in development success rate, complication of manufacturing processes, more strict examination by regulatory bodies, etc. As a result, soaring prices of new pharmaceuticals cannot be contained, and this has become a factor that puts pressure on government finances. The conventional-type pharmaceutical development model which had grown for several decades has already collapsed. In such a situation, one of the possible responses for the time being would be to make the R&D process more efficient through the use of ICT (supercomputers, AI, Health Tech). However, pharmaceutical companies should pursue not only a more efficient process but also a larger market scale.

In the future, pharmaceutical companies should try to convert themselves to health-care companies engaged in "preemptive/precision medicine." This is a new challenge into the area of "prevention" that pharmaceutical companies haven't tried to address in the past, and the following two points will lead to success, I believe.

(a) *Building up an infrastructure for collecting evidence concerning "prevention" – real-world data.*

It is difficult to collect evidence for "prevention" through large-scale randomized trials. When a parent population is created for "prevention" on the basis of Fisher statistics, we will need to follow up a huge parent population of a million to ten million people for a long time, inevitably incurring considerable costs, which will be unrealistic. A promising alternative would be to use "big data." The quality of data is what matters most to extract appropriate results from big data.

In such case, pharmaceutical companies will be required to coordinate with ICT companies and the government and to collect various data on the health and diseases of people (including the use of wearable devices). Then, analytical technologies for big data (Bayesian statistics, artificial intelligence technology, etc.) will need to be sophisticated. A research infrastructure that will make possible the collection and use of such data will be the source of the competitive capacity for creating "prevention" technologies in the future.

(b) *Development of prevention technologies.*

New ideas for "prevention" technologies should be sought from free and creative research in academia. As a role of pharmaceutical companies, the importance of strategic R&D investments aimed at academia and the judgment for promising "preemptive/precision medicine" seeds will increase further. Additionally, developments for commercialization and evaluation tests/clinical research pharmaceutical companies are skillful at will maintain their importance. Research at the precompetitive stage such as the establishment of safety markers, etc., required for evaluation tests will be effectively carried out through the joint research platform system composed of multiple pharmaceutical companies, regulatory agencies, etc., in a unified fashion.

5.2.2 Research Systems and Regulatory Science that Should Be Established in Japan

(a) Establishing a core institution for "preemptive/precision medicine".

Compared with conventional-type R&D on treatment, the research on "preemptive/precision medicine" takes longer. The time lag from the time when a symptom emerges until the disease onset, advancement in severity or paroxysm, etc., is considerably different depending on the disease involved. For example, while the time from symptom onset to a paroxysm tends to be shorter in the case of cardiovascular

disease, the time length for dementia and diabetes tends to be longer, i.e., several years to several 10 years.

Therefore, research should also be pursued from a medium- to long-term point of view. In addition, a core institution to promote such research with a sense of mission and responsibility should be established. Such a core institution is required to set priority issues from a medium- to long-term point of view and to carry out cross-cutting R&D beyond the confines of the relevant domestic ministries and offices. Maximization of the research results will be expected as a whole if each region of the country promotes research in competition for new ideas and the progress is grasped and coordinated by the core institution. Moreover, the core institution is also expected to make active efforts for establishing a system of cooperation between Japan and Europe, the USA, China, etc.

(b) Regulatory science for "health foods".

As for "health foods," discussions on regulatory science as one of the disease prevention technologies are required. In recent years, regulations on "health foods" have been enacted in Japan one after another. However, the "health foods" meeting the minimum rules of the current regulations can't be expected to enhance people's QOL in an ensured manner.

The "health foods" industry is, like the automobile industry, the household electrical industry, etc., one of the industries Japan has strength in. People can directly feel the usability in the case of devices and components like automobiles, refrigerators, smartphones, etc. On the other hand, the effect of "health foods" often depends on the advertising statements of companies, and people can't easily feel their direct usability when compared with the abovementioned devices and components. For this reason, strict regulations should be enacted, and related products should be approved only when the companies concerned respond to the genuine wish of people to be "in good health." Further, a system should be established to allow only those "health foods" actually having preventive effects be delivered to people.

(c) Staffing develop of human resources.

There is a considerable lack of experts in big data and research on epidemiology. Research on epidemiology requires human resources familiar with the know-how of establishing cohorts and maintaining a high follow-up rate for a long time. In addition, like research on epidemiology and life science, etc., all research is flooded with big data. We will need to cultivate and secure bioinformaticians who can analyze such big data appropriately and find meaningful results.

The type of human resources Japan decisively lacks is researchers evaluating health, the economy, and society impacts. It is essential to appropriately evaluate such health, economic, and social impacts for the sustainable development of our society in the future. As a place for cultivating human resources, it will be possible to set up a university, etc., providing courses in public health. Development of better methodologies and case studies should be promoted in universities under the leadership of Japanese or foreign experts specializing in the evaluation of medical technologies. In parallel with this effort, a system for

reflecting evaluation results in national policies should be established, and the career paths (academic posts, administrative officials, R&D companies, think tanks, etc.) should be clarified.

At present, only a few Japanese researchers pursue research on DOHaD, being acutely aware of its significance. However, as the level of Japan's basic research on life science is world-class, this research is expected to attract many participants who recognize the importance of this field, and the world's top-level research will be advanced further.

5.3 Measures for the Social Dissemination of "Preemptive/ Precision Medicine (Including DOHaD)"

5.3.1 Social Implementation of Research Results: A System for Fostering and Maintaining "Motivation"

At the start of the twenty-first century, R&D investments increased rapidly in Japan, and various disease prevention, diagnosis, and treatment technologies emerged. However, no better society will be realized just by establishing disease prevention, diagnosis, and treatment technologies. In Japan, effective disease prevention, diagnosis, and treatment technologies are not used appropriately for the enhancement of people's QOL, just like "pearls thrown before swine." R&D will be required also in the future. At the current stage, however, not just R&D, but a scheme for providing the results of R&D to people requiring them in an appropriate manner should be discussed and implemented in earnest.

An important keyword for the social dissemination of prevention is "motivation." Efforts to foster and maintain the "motivation" of both the provider side and the implementing side of prevention will be needed.

At present, it has become a serious issue in Japan that people having a chronic disease and attending hospital don't respect the drug administration rules laid down by the doctor (medication compliance). Reasons for this behavior may include "unintentionally forgetting to take the drug," "stopping to take the drug through the patient's own judgment," etc., but in the background lies technical problems in medication methods and the frequency, etc., as well as the lack of awareness of the disadvantages of not taking the drug, etc.

"Preemptive/precision medicine (including DOHaD)" targets the stage available for disease prevention. Therefore, compared with the abovementioned people having a chronic disease, it is more difficult to foster and maintain the "motivation" of these people not taking drugs. However, this problem cannot be avoided to realize a better society, and we will have to settle down to work on solving the problem.

In this section, I describe the "R&D" and the "establishment of a system" concerning "motivation," which, I believe, is the essence of disease prevention.

(a) R&D: pursuing stratification/individualization and convenience/usability.

Those involved in R&D should be acutely aware of the direction to foster and maintain people's "motivation."

In the past, general disease prevention methods for the people as a whole were to have adequate meals and physical exercise as well as to quit smoking, etc. While these are effective disease prevention methods, the problem was that only a part of the people who were highly conscious of disease prevention put them into practice. However, when a very safe and highly effective disease prevention technology stratifying/individualizing people is developed, "a highly effective disease prevention method you should carry out" will be clearly shown. Further, it will also show "yourself in the future" when you haven't carried out any prevention methods. As a result, many people will be able to recognize that prevention is an important issue you should address and carry out disease prevention with high motivation, I believe.

Various technology development paths can be conceived to maintain "motivation." For example, technology will be effective that allows the relevant person to feel a sense of accomplishment, such as by quantitatively visualizing the change in his/her physical constitution caused by disease prevention behavior with a biomarker, etc. Or, another disease prevention technology which provides a sufficient disease prevention effect by means of an easy-to-administer form (injection medicine, internal medicine, etc.) and a small number of administrations in a short term will also be effective. Moreover, in order to prevent a "failure in taking" disease prevention drugs, a different system will also be effective which automatically senses the completion or non-completion of drug administration and gives an alert, etc., when a "failure in taking" drugs occurs (e.g., ICT technology used for Abilify MyCite®). New technology called "digital medicine" has appeared, to realize healthcare management and prevention by smart phone application (e.g., Blue Star®)

(b) Systems: setting up a sustainable system, including incentivization for those concerned.

Social systems such as relevant schemes and regulations, etc., should be prepared for the provider side of prevention (industry, government, community, etc.) in order to allow the result of R&D to be delivered to each person.

Compared with general disease treatment methods, the short-term effects of prevention is invisible. Similarly, it will also be difficult, I believe, to feel the long-term effects, such as that "the relevant person wasn't taken ill." Incentivization will be required for each person to maintain high motivation and to carry out the methods steadily without getting tired of them. One direction for that purpose will be giving material or pecuniary rewards, commendations, etc., in each community provided on the basis of the evaluation of the effort and disease prevention behaviors of each person. However, ingenuity is required to prevent these rewards from being the very objective and to get people to understand that their health itself is the biggest reward of all in a skillful manner. For this purpose, it is important that the benefiting people understand disease prevention through education on health at various stages of their life, i.e., in high school, in university/college, in society, etc.

In the past, medical treatment was provided by medical institutions. However, for the purpose of prevention, elaborate and original efforts of various persons and organizations concerned will be expected, such as corporate health insurance societies, private insurers, pharmaceutical companies, health-care companies, etc. Activities not just depending on the government for financial resources and establishment of systems but involving the private sector will be a driving force for spreading disease prevention in the medium to long term.

[Column 3] Future form of the insurance system

The existence of the medical insurance system for the whole nation that Japan boasts is, conversely, also one of the factors for reducing the motivation for prevention. In the USA, 60% of all bankruptcies are caused by the inability to pay for medical expenses. In Japan, however, everyone can receive low-priced medical treatment. This fact has led to the tendency of people in Japan to feel that "Even if I should fall ill without paying attention to disease prevention and then the disease should worsen, I can visit the hospital and consult the doctor." The system of medical insurance for the whole nation should be maintained firmly in the future, but in respect of prevention, we should study a new framework for a different insurance system.

Here, I'd like to describe the medical insurance system for the whole nation, which is one of the social systems that can be involved in disease prevention. In the first place, the medical insurance system for the whole nation is a system established under the concept of supporting the medical expenses of people suffering from diseases by the whole nation contributing their share of the costs. (As a matter of fact, the financial resources depending only on the collection of insurance premiums are considerably insufficient, and a huge subsidy is provided from tax revenues.) However, since prevention targets almost all the people, it won't be appropriate that the system of medical insurance for the whole nation based on the spirit of mutual aid plays a central role in it. Moreover, it will also be unrealistic to make the government shoulder the burden of all costs of prevention, considering the tight financial condition. For this reason, the cost could be covered, for example, by private insurance. In that case, improvement of the profit of insurers is directly connected with the disease prevention behavior of the insured. For instance, it is conceivable as a method for the insured to provide information on disease prevention, to give rewards when disease prevention is successful, and to set up a scheme for adequately evaluating daily disease prevention behavior, reflecting the result in the insurance fee (implementing disease prevention = reduction of insurance fee), etc.

[Column 4] Stealth health care: What the next-generation public health ought to be

It is difficult to persuade everyone to change their behavior by just incentivizing prevention. On the other hand, sufficient evidence has been obtained, and "stealth health care" is effective as a disease prevention scheme that should be provided to everyone.

"Stealth health care" assumes a mechanism for everyone to carry out prevention activities unconsciously by incorporating prevention methods in social systems in a natural manner. To give an example, in the USA, while excessive consumption of

salt content has become an issue, it has been revealed that more salt content is contained in processed foods than in bottled table salt. To avoid the excessive intake of salt, it will be more effective to strengthen regulations on the use of salt in processed foods than to ask each of us to make an effort not to take too much salt in our everyday life. In the USA, from the viewpoint of DOHaD, nutrients that tend to be insufficient are selectively blended additionally under a food aid program for families on relief with pregnant women or infants.

As such a scheme involves incorporation in social systems and many people enjoy the fruits of such scheme unconsciously, collection of sufficient evidence and consensus building among those concerned are needed before introducing it. R&D and discussions for this purpose, I believe, will be important objectives Japan should pursue in the future.

5.4 Future Vision 2040

5.4.1 Life-Course Health Care

Here, I'd like to describe the future vision of health and medical care through 2040. The emerging central concept of "life-course health care" means physical and mental care from the viewpoint of the lifetime of humans. It is the direction Japan should pursue in the future to realize all social needs (enhancement of QOL, industrial vitalization, and optimization of medical expenses/care expenditure).

First, the entire genome information will be analyzed at the time of birth. Then, information on lifestyles (meals, physical exercise, etc.), biomarkers (molecules contained in the blood/urine and images), medical checkups, clinical information (electronic charts, statement of medical expenses, etc.), and so on is collected over a lifetime on a periodical basis. These data groups are managed in the domestic database. Under a management system which strikes a balance between security and convenience, academia, government, and companies proactively utilize the database. Analysis of the database not only deepens the understanding of life phenomena but also accelerates the R&D on "preemptive/precision medicine (including DOHaD)." The result of research will be provided to people not only through medical institutions but also through various organizations such as health insurance associations, private insurance companies, pharmaceutical and health-care companies, etc. It is expected that tips for further R&D can be obtained, and additional basic research will be developed when people actually comply with the principle of "preemptive/precision medicine (including DOHaD)."

By accelerating these cycles, a paradigm shift will occur from the current medical measures focused on cure (treatment, symptomatic therapy) to care (prevention of disease onset, prevention of advancement in severity, prevention of paroxysms and recurrence). Then, the targets for care will be increased from the past main target of the aged population to include the youth and from the viewpoint of DOHaD, babies, and infants. Additionally, even if "preemptive/precision medicine (including DOHaD)" progresses further, many people will face important issues like nursing

care, the terminal phase, etc., sooner or later (*[Column 5]*). By also holding discussions on such matters and proceeding with consensus-building efforts, we will be able to realize physical/mental care from the standpoint of a lifetime, from before birth to the terminal phase, I believe.

[Column 5] How the terminal phase ought to be managed

Even if "preemptive/precision medicine (including DOHaD)" makes dramatic progress in the future and health problems are considerably improved, the "terminal phase" coming at the end of a lifetime cannot be avoided. We have many ups and downs in our lives in respect of health, social activities, human relations, etc., but "all's well that ends well."

In Japan, the response to the "terminal phase" has just begun. Since the latter half of the 2000s, formulation of guidelines has progressed rapidly on what terminal care ought to be, led by the societies for emergency medical services and palliative medicine, etc. In the future, we will need to carry out further activities recognizing consensus building in Japan and to make efforts, including legislation. In parallel with such rule-making efforts, it will also be important that each one of us prepare for the terminal phase of our lives at an early stage.

Approaches of science and technology are also effective for managing the "terminal phase." For example, by analyzing the big data on terminal care (electronic charts, etc.), it will be possible to measure the effect of terminal care, e.g., quantification of pain, etc. Additionally, various indications useful for terminal care will also be obtained from the huge amount of electronic charts of dead people (Figs. 5.4 and 5.5).

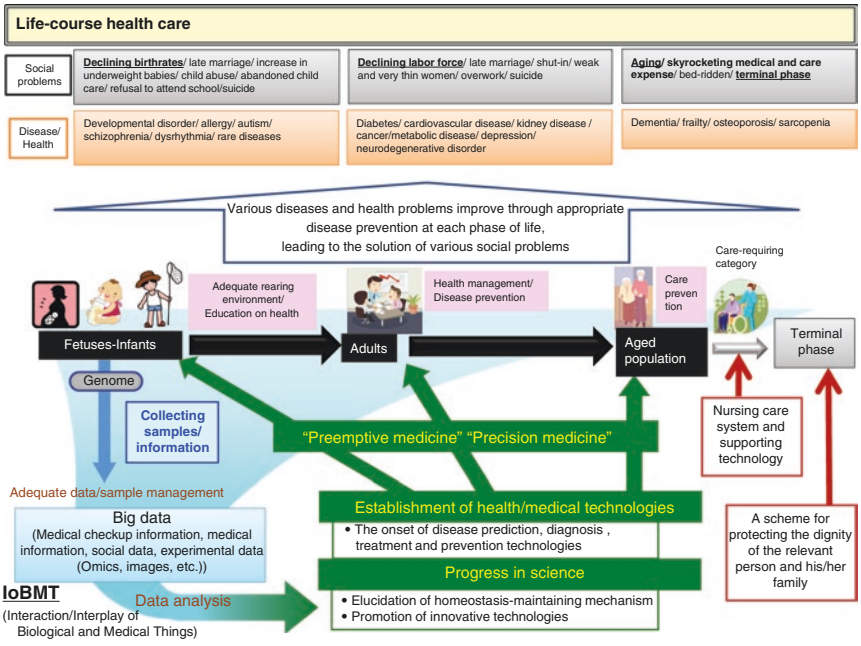

Fig. 5.4 Life-course health care (A future vision for 2040)

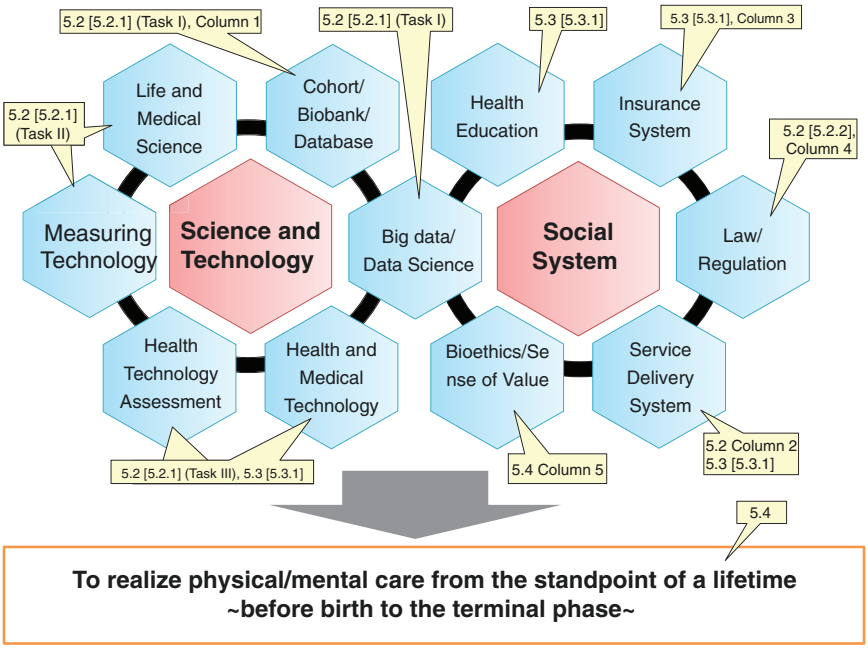

Fig. 5.5 Strategic framework to realize life-course health care

5.5 Personal Opinion: Expectations for "Preemptive/ Precision Medicine (Including DOHaD)"

Finally, I'd like to mention my expectations for "preemptive/precision medicine (including DOHaD)."

Even if "preemptive/precision medicine (including DOHaD)" technologies are established, the society where these are introduced forcibly without regard to the intentions of the people would be "unhealthy." We should enjoy risks in our lives, I believe. A "healthy" society will be one where we are permitted to devote our all time to hobbies and occupations, eat tasty food to our heart's content, and indulge in dangerous amusements while risking somewhat unhealthy behavior.

I believe that "preemptive/precision medicine (including DOHaD)" is just one of many options in our life. We have to make choices one after another in our lifetime, and it will lead to a happy life, I believe, if we continue to make choices that seem best for ourselves, while weighing various things in the balance. We should not set the goal of "preemptive/precision medicine (including DOHaD)" to the realization of insipid health and long life. I hope its concept will be warm-hearted, with the primary objective being to support people's happy lives. Based on such recognition, I will lead Japan to a wonderful future through its R&D strategy for realization, as well as surveys, proposals, and implementation of social dissemination methods.

5.6 Conclusions

In order to realize "preemptive/precision medicine (including DOHaD)" and "life-course health care," we must implement various R&D themes and infrastructure development. But there is no time. Compared with the USA and the EU, it is hard to say that measures in Japan are progressing. We must implement them as soon as possible and open up a bright future for Japan. Therefore, as a member of Japan's public think tank organization, I would like to continue appealing to the government about the direction that science and technology policy should be.

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References

1. Ministry of Health. Labour and Welfare homepage. http://www.mhlw.go.jp/
2. WHO. THE GLOBAL BURDEN OF DISEASE -2004 update, etc.
3. JST-CRDS. Strategic initiative: promotion of preemptive medicine in the Super-Aged Society. 2010.
4. JST-CRDS. Strategic proposal, promoting life course health-care: importance of preemptive medicine in pregnancy to child hood. Center for Research and Development Strategy; 2014.
5. The WHITE HOUSE PRESIDENT BARACK OBAMA "The Precision Medicine Initiative". 2015.
6. Gluckman PD, Hanson MA. Living with the past: evolution, development, and patterns of disease. Science. 2004;305:1733–6.
7. WHO. Global Database on Body Mass Index.
8. OECD. Health at a Glance 2011.
9. JST-CRDS. Strategic proposal, integrated promotion of human microbiome study: new development in life science and health care. 2016.