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Present State and Advances in Personalized Medicine
— Importance of the Development
of Information Service Systems for the Public —

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1 | Introduction

The International Human Genome Sequencing Consortium, which launched the Human Genome Project in 1990, announced a draft sequence of the human genome in cooperation with Celera Genomics in 2001[1,2]. The consortium released the finished version of the sequence[3] and announced the completion of the project in October 2004.

The complete human genome sequence was obtained using DNA samples taken from only a few people. The completion of the project led to the post-genome era, and the next important task is to apply the genome information of each individual to medicine and promote personalized medicine.

This article discusses advances in pharmacogenomics[*1] and molecular-targeted anticancer drugs[*2], both of which are rapidly evolving technologies, and suggests future initiatives to achieve social acceptance and public understanding of personalized medicine through the provision of genome-related information to the public (Figure 1). These issues need to be addressed to successfully promote personalized medicine.

Figure 1 : Outline of this article
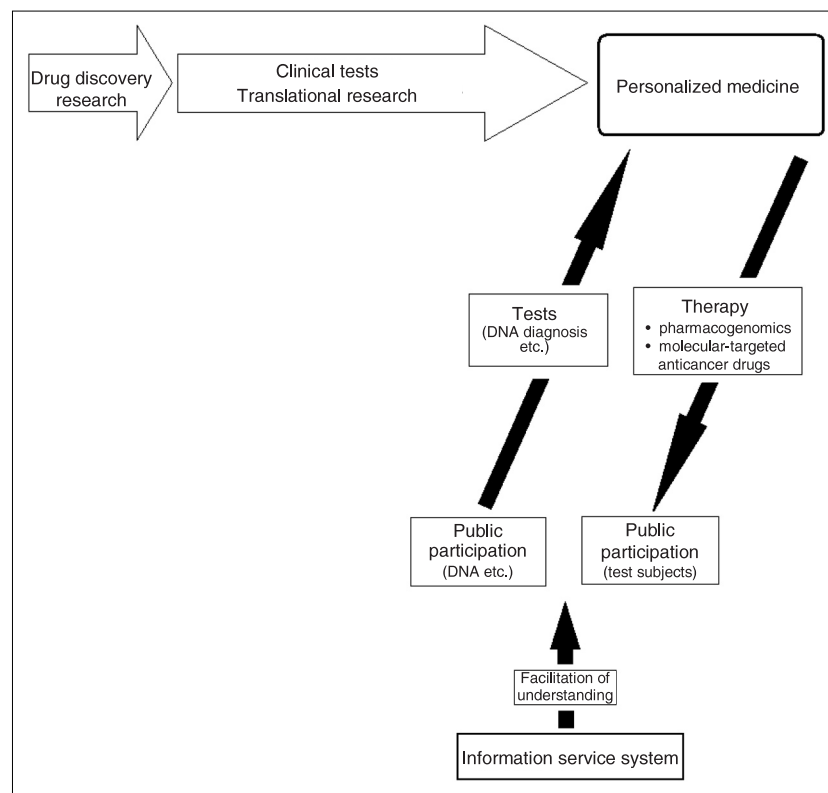
2 | Personalized medicine

2-1 About personalized medicine

In Japan, "personalized medicine" is sometimes called "kobetsuka iryou", which is a direct translation, or "order-made iryou", which is a Japanese-English phrase. All of these terms describe the implementation of medicine (prevention, diagnosis and therapy) based on genome information including molecular/genetic data or molecular/genetic aberrations responsible for diseases and symptoms.

In conventional medicine, doctors chose drugs and the method of administration (dosage and frequency) based on their experience and opinions (so-called "doctor's prescription"). The differences in drug efficacy and side effects among individuals were vaguely explained by the difference in their "constitutions". However, as the need for evidence-based medicine became more widely acknowledged, doctors began to place emphasis on scientific validity when choosing therapeutic strategies. Scientific validation at a molecular level requires a vast amount of research using the results from the genome project and post-genome research. This implies that we have entered a stage where we now recognize that the difference in "constitutions" is in fact the difference in genes and genome information. (In this paper, the term "molecule" principally refers to a DNA, RNA or protein. The term "genome" originally referred to the entire set of genes, but since many biological phenomena involve DNA regions other than genes, the term "genome" used here refers to an individual's complete set of DNA. Thus, "molecular data" includes all the information provided by the DNA sequence, mRNA expression, protein expression, etc., and the measurements and analyses of these data are referred to as "molecular diagnoses".)

In parallel with the progress of the genome project, the concept of "genome-based drug discovery" has attracted attention in drug R&D. This concept aims at the development of drugs that target the molecules responsible for diseases. Pharmaceutical drugs that are developed through genome-based drug discovery

potentially show high specificity compared to conventional drugs and are therefore expected to reduce the risk of side effects and increase their therapeutic efficacy. Reduced risk of side effects is an especially important issue, as side effects were found to be the fourth to sixth most common causes of death in the U.S. [4]. According to research reported in 1998, in the U.S., approximately 2.2 million (6.7%) of hospitalized patients suffered from severe side effects, 110,000 (0.32%) of whom died. Thus, the realization of personalized medicine is an extremely urgent task to reduce the side effects of drugs and secure public safety.

Personalized medicine provides appropriate treatment to patients based on the difference in genome information or molecules responsible for diseases (Figure 2).

"The five rights" is a slogan originally intended to remind nurses of the points to be confirmed at injection or administration of drugs to patients, but it is also relevant to the concept of personalized medicine.

The minimum standard of practice for medication administration is checking "the five rights" to provide patient safety.

The Five Rights:
- Right Patient
- Right Drug
- Right Dose
- Right Time
- Right Route

"Right patient" and "right drug" imply the use of molecular-targeted drugs developed through genome-based drug discovery, i.e. the recognition of molecular aberrations responsible for diseases or symptoms and the administration of drugs that exclusively act on and remove aberrations. "Right patient" and "right dose" imply the importance of pharmacogenomics in drug-metabolizing enzymes etc., discussed in the next chapter, i.e. prescription of appropriate dosage based on the difference in drug response among individuals. In addition to drug-metabolizing enzymes, steps such as drug absorption, distribution, metabolism and excretion (ADME) all play an important role in drug metabolism. "Right dose", "right time"

Figure 2 : Personalized medicine
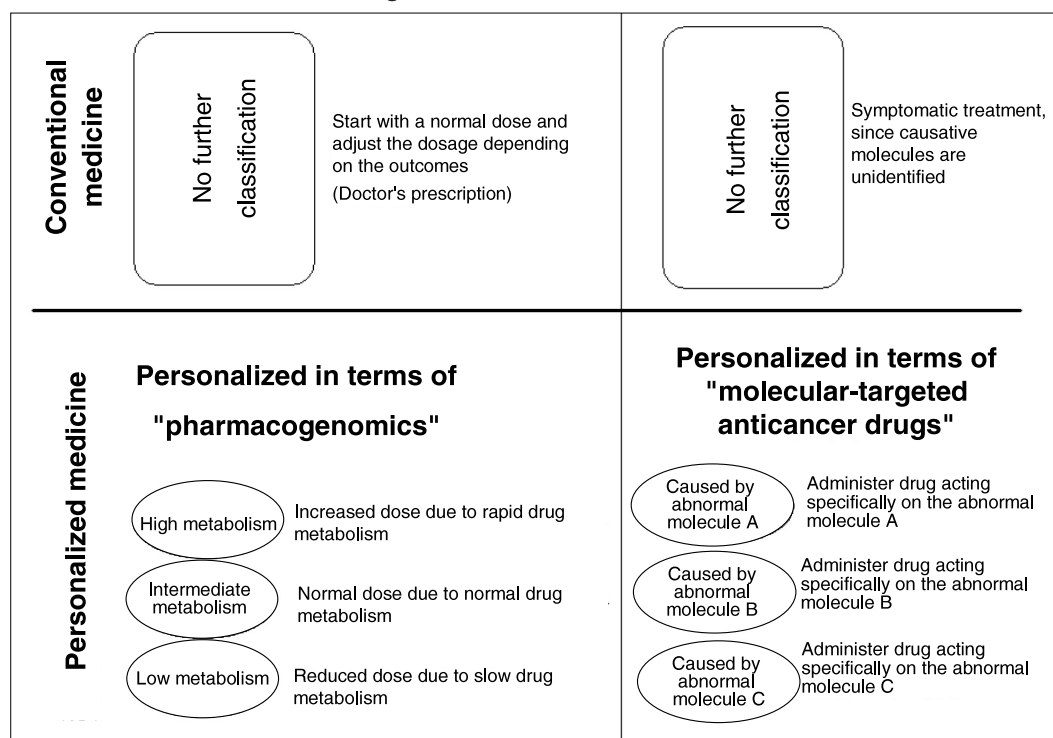
and "right route" are therefore important factors to consider in understanding the difference in ADME among individuals.

2-2 Pharmacogenomics

The Food and Drug Administration (FDA) announced a draft plan for "Guidance for Industry, Pharmacogenomic Data Submissions" in November 2003 and its final plan in April 2005. In response to the FDA's action in June 2004, the Evaluation and Licensing Division of the Pharmaceutical and Food Safety Bureau in the Ministry of Health, Labour and Welfare recruited opinions and information from pharmaceutical makers on the current status of clinical trials using genome tests and announced "Submission of information to government agencies for the preparation of guidelines for the application of pharmacogenomics to clinical trials of drugs" (Notification No. 0318001 from the Evaluation and Licensing Division of the Pharmaceutical and Food Safety Bureau) in March 2005. These actions imply that pharmacogenomics has progressed from the research stage to the practical stage, and now requires data submission for application to clinical drug trials.

Pharmacogenomics is defined as the analyses of drug response based on the genetic data of individuals. It is a system to predict and assess the difference in drug efficacy and side effects among individuals (conventionally explained as "constitutions") based on the results of comprehensive and systematic analyses of genome information. The typical research targets of pharmacogenomic studies are the SNPs (single nucleotide polymorphisms) found in the drug-metabolizing enzyme genes CYPs (cytochrome P450). Various molecules involved in *in vivo* kinetics, such as excretion and uptake of drugs (pharmacokinetics), also affect drug efficacy and side effects and are therefore subject to pharmacogenomic studies.

As in the case of Iressa, which will be discussed below, the difference in genes encoding drug target molecules on which the drugs directly act can be correlated with the difference in drug efficacy. Pharmacogenomics of drugs, drug target molecules and the downstream signaling pathway are as important in drug development as that of drug metabolism and dynamics.

A SNP is a single DNA base pair variation shared by a human population greater than a certain size. SNPs occur at a frequency of 1% or higher in the human population and are distinguished from mutations that occur at a lower frequency. In 1999, the SNP Consortium

Figure 3 : SNPs
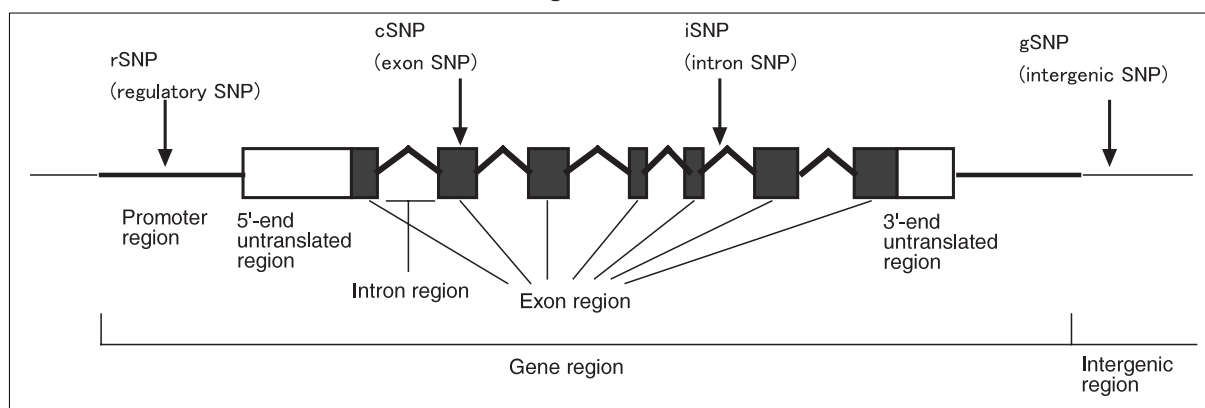
was established by the Wellcome Trust and approximately ten pharmaceutical and technology companies. Their research work and many other SNP projects have revealed that SNPs are evenly distributed across the genome at a frequency of one SNP per 100-1,000 bp, i.e. there are 3-10 million SNPs in the entire human genome. SNPs found in gene regions that encode proteins or promoter regions that regulate gene expression exert various changes in phenotypes (Figure 3). Thus, SNPs in the above-mentioned CYPs possess considerable clinical significance in terms of drug metabolism. European countries and the U.S. FDA approved DNA chips to identify SNPs in CYPs as ex vivo diagnostic agents in September and December 2004, respectively. Moreover, it is known that the development of side effects of the anticancer agent Camptosar is related to the difference in the activity of its metabolic enzyme (conjugating enzyme UGT1A1). Since the activity of the enzyme is affected by SNPs in the transcriptional region of the gene encoding the enzyme, the FDA revised the labels attached to this anticancer drug in July 2005 and included the list of relevant SNPs and directions for dosage regulation based on the enzyme activity of patients[5]. Regarding the current state of SNP research in Japan, R&D of SNP analysis techniques and research on the involvement of SNPs in diseases are currently being conducted at the SNP Research Center of RIKEN and the Institute of Medical Science of the University of Tokyo[6, 9].

2-3　Molecular-targeted anticancer drugs

Pharmacogenomics uses genome information to analyze the *in vivo* delivery process of drugs, from their ingestion to their arrival at the target molecules. In contrast, "genome-based drug discovery" uses genome information to discover the molecules responsible for diseases and develop drugs (molecular-targeted drugs) targeted at these molecules.

Together with the progress in the Human Genome Project, causative genes of diseases have been vigorously searched for and analyzed. In particular, cancer-related research has advanced rapidly due to the timely integration of clinical research with basic research; for example, research on the mechanism of cancer development was integrated with cell cycle and intracellular signaling mechanism studies, and research on the action mechanism of anticancer agents was integrated with studies on DNA replication, cell division and cell death induction. The results of these studies led to the development of the first anticancer drugs based on molecular mechanisms. To date (as of July 2005), four molecular-targeted anticancer drugs have been approved and used in Japan; Herceptin (breast cancer), Rituxan (B cell non-Hodgkin's lymphoma), Glivec (chronic myeloid leukemia CML and gastrointestinal stromal tumor GIST) and Iressa (lung cancer), all of which were developed by U.S. or European pharmaceutical companies (Figure 4).

These molecular-targeted anticancer agents act on different target molecules through different mechanisms (Herceptin and Rituxan are antibodies and Glivec and Iressa are kinase inhibitors), but were all developed through a common drug development strategy. Each of

Figure 4 : Molecular-targeted anticancer drugs
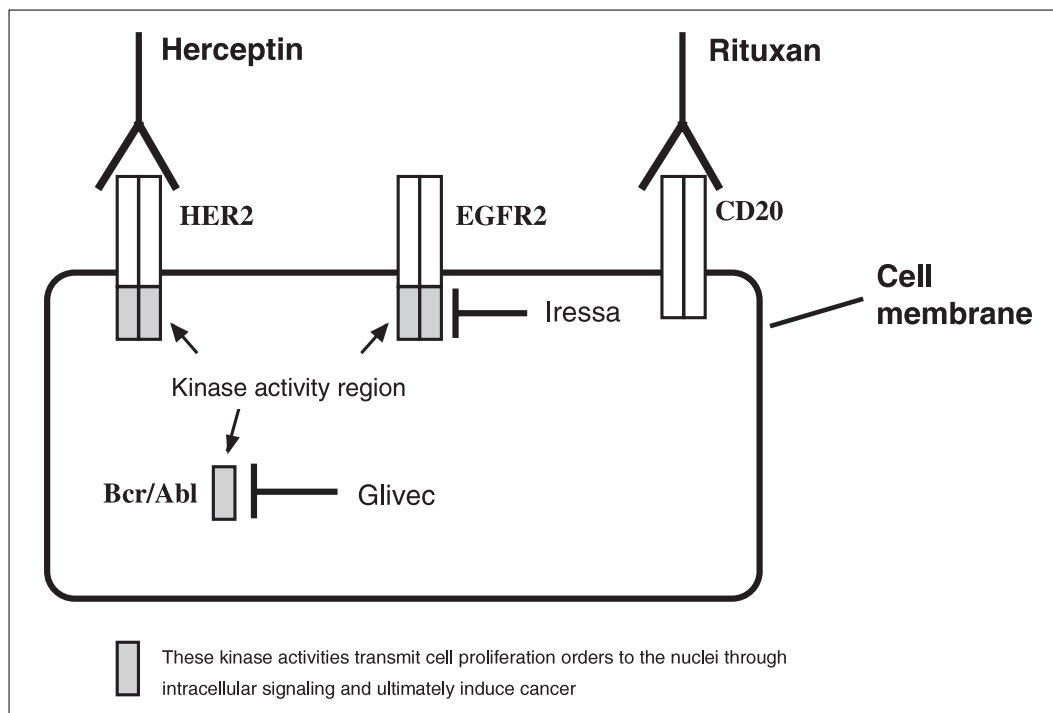
these drugs target molecular aberrations that are specific to each disease and act exclusively on patients that possess the aberrations.

Herceptin is an antibody that recognizes HER2, a growth factor receptor that penetrates the cell membrane. After recognizing and binding to HER2, which is located on the surface of cancer cells, Herceptin activates the antibody-dependent cell damage mechanism and specifically exerts an antitumoral activity on HER2-expressing cancer cells. Rituxan is also a specific antibody that recognizes the CD20 antigen, which is specific to some tumors. Glivec exerts antitumoral activity on chronic myeloid leukemia (CML) through the inhibition of Bcr-Abl tyrosine kinase, which is encoded by the Bcr-Abl gene, a causative gene of CML produced through chromosomal translocation. The drug also inhibits KIT tyrosine kinase and therefore exerts an antitumoral activity on KIT-positive gastrointestinal stromal tumor (GIST). Iressa acts through a mechanism similar to Herceptin and inhibits the kinase activity of EGFR, another growth factor receptor that penetrates the cell membrane.

In order to choose the "right drug" and the "right dose", confirmation of the molecular information of each patient is a prerequisite to implement personalized medicine. Thus,

molecular diagnosis is indispensable for the appropriate use of molecular-targeted drugs or drugs whose metabolism depends on SNPs of CYPs.

This is also implied by the indications attached to these drugs; Herceptin "should be used for metastatic breast cancer patients with HER2 overexpression", Rituxan "should exclusively be used for CD20-positive patients confirmed through immunohistological staining or flow cytometry", and Glivec "should be used for patients diagnosed chronic myeloid leukemia through chromosomal or genetic screening or KIT-positive gastrointestinal stromal tumor through an immunohistological test". Before using these molecular-targeted anticancer agents, immunohistological tests or chromosomal or gene screening must be performed to confirm whether their administration is appropriate.

Described below is an episode that demonstrates the importance of pharmacogenomic analysis of target molecules of anticancer agents to confirm the adequacy of anticancer agent administration.

In July 2002, Iressa was approved as a therapeutic agent for lung cancer in Japan before approval in any other country. The drug exerted high anticancer activities including cancer regression in some patients, but often induced

severe side effects such as interstitial pneumonia. Later, the drug was concluded to have "no survival advantage" based on the results of the first analysis of a worldwide clinical trial.

However, in April 2004, it was reported that the drug was highly effective in patients that have mutations in EGFR, the target molecule of Iressa[7, 8]. In Japan, extensive research on gene expression and SNP analysis for the prediction of drug response and side effects of Iressa are being performed, with the main initiative carried out by the Institute of Medical Science of the University of Tokyo [9]. Arguments concerning the efficacy and approval of the drug are not relevant to this report and will not be discussed here any further. Nevertheless, the emphasis placed on genetic diagnosis to detect mutations in the target molecule of Iressa demonstrates that personalized medicine has already been implemented in the form of genetic diagnosis in the clinical setting.

2-4　Translational research: clinical studies

Cancer therapy using molecular-targeted anticancer agents and medication regimens based on pharmacogenomics present an excellent opportunity to return the outcomes of scientific research to the public. That is, the results of basic scientific research are utilized for drug discovery and then fed back to clinical practice.

Advances in molecular biology have elucidated development mechanisms of many diseases, and drugs that target these mechanisms or molecules involved in these mechanisms have been intensively researched and developed worldwide. A drug for which the efficacy has been demonstrated *in vitro* will not be approved as a drug until its *in vivo* efficacy has been demonstrated in the human body.

Drug efficacy in the human body was conventionally demonstrated in clinical trials conducted by pharmaceutical companies for commercialization of drugs, but the revision of Pharmaceutical Affairs Law has also enabled researchers to conduct clinical trials. Moreover, systems to facilitate translational research that bridges the gap between basic research and clinical research have been improved[10].

Since drug efficacy ultimately needs to be confirmed in humans, not only clinical trials of drug candidates, but also epidemiological research including genetic analysis must be actively promoted. Furthermore, the high sensitivity to Iressa seems to be associated with "Japanese (Asian)" and "females". In consideration of such "genetic difference among races" and "genetic difference among sexes", we should perform genetic analysis and research locally and avoid the direct application of research results obtained in the U.S. and European countries to the Japanese population. Genetic differences among races must be considered by conducting bridging studies with Japanese subjects to confirm the validity of data obtained from clinical trials conducted overseas. Indeed, a drug has been described that has been demonstrated to be effective only in a particular race (African-American)[11], but was nonetheless approved by the FDA in June 2005.

When predicting drug response in individuals by genetic diagnosis, the current subjects of pharmacogenomic studies are drug-metabolizing enzymes, such as CYPs, the function and clinical significance of which are already evident. In addition, factors involved in pharmacokinetics, drug target molecules (as in the case of Iressa sensitivity) or factors involved in the signaling of target molecules are also potential subjects for pharmacogenomics. Such subjects include genetic variation in EGFR, the molecular mechanism of which is unknown, but has recently been found to contribute to drug efficacy, and many other molecules affecting the effects of drugs that are yet to be discovered.

Prediction of drug response based on molecular information involves many unknown factors and requires further research. In order to translate these research results into medicine, translational research is indispensable for demonstration research in human clinical research.

3 | Public understanding for personalized medicine

3-1　Genome information as personal information

"Genetic information" could be regarded as the ultimate form of personal data but differs greatly from other personal data in many

ways. With the current state of science and technology, an individual cannot easily access his or her own genetic information. It can never be rewritten and is also transferable among family members, a fact demonstrated by the existence of familial disorders. The biggest problem is "the uncertainty of science" ; the implications of genomic information have not been fully understood but may have a great impact on the life and health of individuals. This indicates that, in the current situation, genetic analysis technology represented by DNA sequencing and SNP analyses goes far ahead of the scientific validation technology required to understand the significance of an individual's genomic information. Basic and applied research for bridging the gap between these technologies should be conducted swiftly but with sensitivity, given the fact that this research is being performed on human subjects. Thus, genome information, where there is still a degree of scientific uncertainty, is more important than ordinary personal data and must be handled with great care. Books written from various standpoints on issues concerning medical science, medicine and personal data should help advance the understanding of these issues[12].

The requirement of making a genetic diagnosis has been stipulated in guidelines for the administration of Iressa and other molecular-targeted anticancer drugs. Genes involved in the development of diseases represented by familial breast cancer, familial adenomatosis coli and hereditary non-polyposis colorectal cancer have been identified. When receiving medical treatment or notification or providing informed consent to the doctor before treatment, each person is required to possess a sufficient knowledge and understanding of genes. The significance of "understanding" is explicitly cited in the ethical guidelines concerning human genome and genetic analysis research[13], which defines "informed consent" (translated as "setsumei ni motozuku doui" — consent based on explanation) as "agreement given voluntarily based on sufficient prior explanation and understanding". In that sense, an open lecture given upon the submission of the FDA's final draft of pharmacogenomics guidelines had the very

suggestive title of "Personalizing your Healthcare: The Best Consumer is an Educated Consumer" [14].

## 3-2　Importance of information provision and public understanding

The handling of genetic information has been stipulated at the policy level through enactment of the above-mentioned Act concerning the Protection of Personal Information and ethical guidelines from individual agencies. The government has proposed measures against bioethical issues, which are inevitably related to genetic information, through the establishment of the Bioethics Committee in the Council for Science and Technology Policy.

The BT Strategy Council has included "thorough public understanding — establishment of a system enabling appropriate judgment and choice by the public—" as one of the three strategies ("research and development", "industrialization" and "public understanding") in the Biotechnology Strategy Outline[15]. This implies that the well-balanced promotion of these three factors is essential to the development of biotechnology areas including medicine and returning favorable outcomes to the public. Such development cannot be achieved without "public understanding" (Figure 5).

"Strategy 3: thorough public understanding — establishment of a system enabling appropriate judgment and choice by the public". This underlines the fact that "no matter how advanced it is, biotechnology cannot improve people's lives without achieving public understanding and acceptance. It is important to establish a system that enables the public to make appropriate judgments and choices concerning biotechnology and to improve social infrastructure to remove the fear and anxiety against novel technologies". The strategy consists of three factors:

(1) Enrichment of information disclosure and provision systems
(2) Display of a firm government stance on safety and ethics
(3) Enrichment of school education, social education, etc.

These factors correspond to infrastructure

Figure 5 : Diagram describing the three strategies
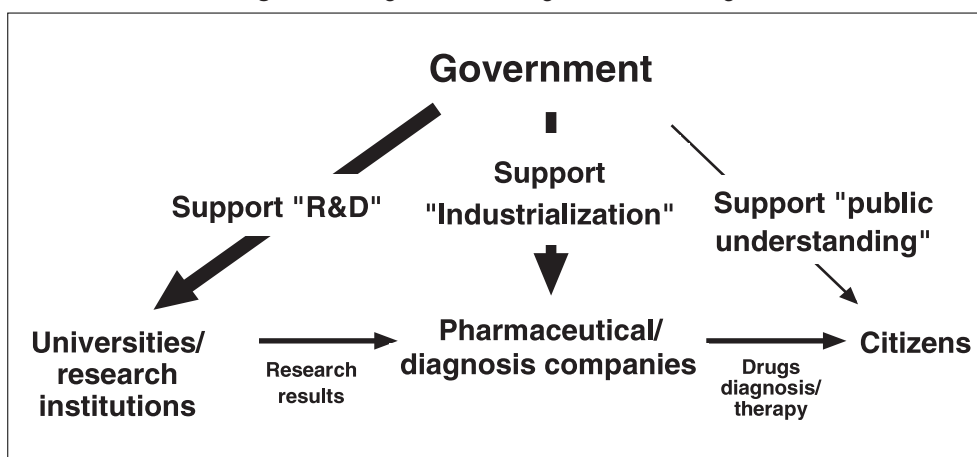
improvement in the areas of "handling of personal data", "bioethics" and "genetic education", which are vital elements for the implementation of personalized medicine.

"(3) Enrichment of school education, social education, etc." emphasizes that "in order to establish an environment where the public can make appropriate judgments and choices, it is important to increase opportunities in school education that allow children to acquire basic knowledge and acquaint themselves with scientific viewpoints and notions and to increase social education opportunities where people can readily learn about science. Moreover, further enhancement of biological education is required in schools, e.g. efforts to increase the number of students enrolled in biology classes in higher education and to increase the opportunities to take biology exams as part of the university entrance exam. In addition, it is important to support a comprehensive, cross-curriculum approach, such as helping students to acquire a science-based understanding of life in the Period for Integrated Study, and to realize the value of life during childhood." However, Japanese high school students are only provided with a basic knowledge of genetics, and information concerning important terms such as "heredity" and "genes", "genetic mutations" and "SNPs", "mutations in somatic cells" and "mutations in germ cells", which are concepts everyone would have to deal with in personalized medicine, is not provided in sufficient detail[16].

In the "Survey on public awareness of science and technology" conducted in February and March 2001[17], 74% of respondents correctly understood the term "DNA". Then, another question was asked to verify how well the respondents understood this term; "In which part of your body can you find DNA?" (multiple-choice question). Only 33% could answer this question correctly. Furthermore, in a series of questions concerning the probability of developing genetic diseases, which is closely related to personalized medicine, only 39% (55% in the U.S.) could answer correctly for all four questions.

Although the importance of public understanding is advocated in the policy, "genes" are still not sufficiently understood by the public. Such lack of public understanding will become an obstacle to the implementation of personalized medicine based on appropriately informed consent and the promotion of public participation in scientific and genetic research and translational research that is the foundation of personalized medicine.

4 | Suggestions

4-1 Current status in Japan

In order to achieve social acceptance of the genetic research that underlies personalized medicine, information services and educational activities which aim at a better public understanding of genes are critical policies that will be required in the areas of science and technology and medicine. Meanwhile, issues concerning genes are not to be left in the hands of doctors or scientists; in personalized medicine, each of us will confront these issues

Figure 6 : Social acceptance of personalized medicine
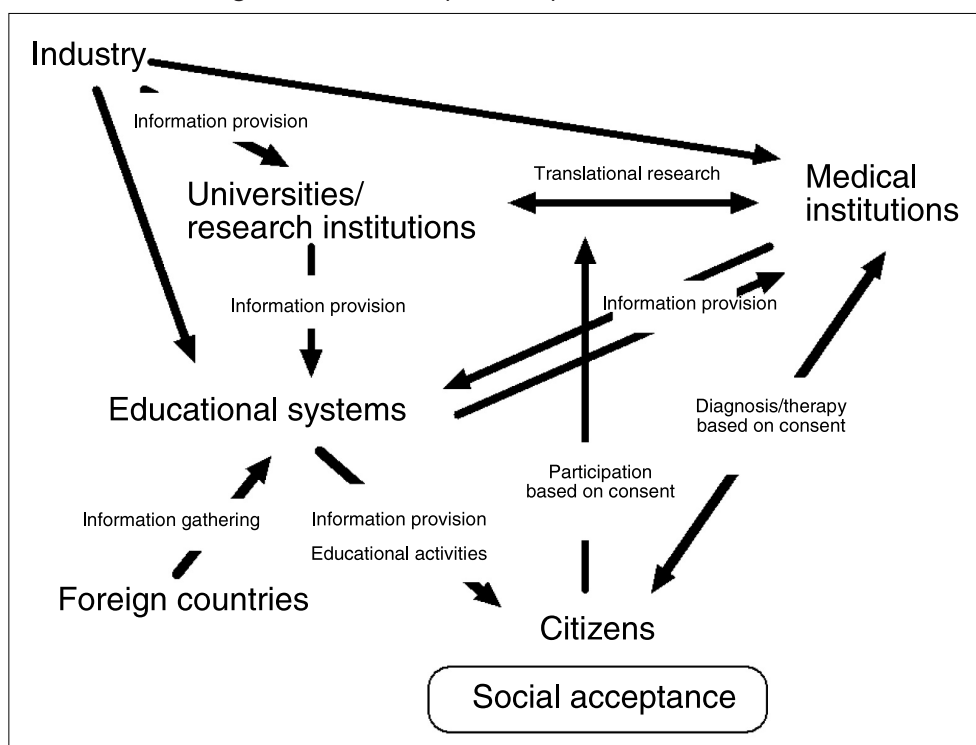
at the point of "self-determination" of our own medical treatment with "self-responsibility", and a lack of understanding could lead to poor "self-determination". Moreover, the realization of personalized medicine requires participation of the public in translational research, i.e. demonstration research. Thus, it is an urgent task to establish a system that includes personnel and organizations that provide public education on "genetics".

U.S. high school textbooks have richer and more detailed descriptions on "genetics" compared to those found in Japanese textbooks [16]. In addition, the Genetic Alliance (formerly known as the Alliance of Genetic Support Groups, Inc.), which is an organization formed from more than 600 bodies supporting gene-related diseases and patients[18], and the National Council on Patient Information and Education, which was established based on the suggestion of the federal government[19], are involved in various activities to support patients, their families and the public who will eventually become medical service consumers. The activities include counseling, educational activities for providing high-quality information, such as the latest research results and scientific information, mediation between government, company and

the public, management and support of patient groups and facilitation of public participation in translational research.

In Japan, we have a clinical geneticist system[20] and a genetic counselor certification system[21] to promote genetic counseling and NPOs to provide genetic education to the public[22], but we still lack an information service system that services the entire nation.

4-2　Establishment of an Internet-based information service system

The above-mentioned survey on public awareness[17] revealed that most people acquire science and technology information "passively" from mass media. In this survey, conducted four years ago, only 12% answered that they actually used the Internet to obtain information, but the Internet was chosen as the most attractive source of information that people would like to use in the future. In consideration of the need to establish a system that services the entire nation, the Internet is one of the most effective routes to provide science and technology information to the public.

Information that needs to be provided to the public is often derived from the latest scientific research results; it is important to immediately

add and revise such research results whenever necessary. The system must allow easy updating of the information, and an Internet-based system would be effective in this regard. The system would also need to be accessible to medical institutions, so that the latest information and therapeutic methods can be made available to the suppliers of medical services.

In order to realize personalized medicine based on genome information, where advances in research and applications (drug development and clinical practice) occur in parallel, information must be sufficiently provided to and understood by the public. Considering the above-mentioned advantages, an Internet-based system seems to be the most effective and feasible way of providing such information.

The information can be divided into two types; (i) specialized information (e.g. explanation of molecules involved in disease development and prognosis and significance, risks and benefits) corresponding to each disease is required for understanding and providing consent when receiving personalized medicine or participating in translational research, and (ii) basic information to serve as the basis for understanding such specialized information. The former requires a system to enable one-on-one counseling or answering questions whenever required, while the latter can be integrated into school education or effectively provided through open lectures. Human resources capable of counseling or responding to the public will be necessary, and systems to develop human resources such as genetic counselors will also need to be established. The establishment of an information service system would also be an effective tool to facilitate, support and supplement such counseling.

Since such an information service system involves interactions between areas such as science and technology, medicine, and school education, it would require a cross-ministry linkage led by the Ministry of Education, Culture, Sports, Science and Technology and the Ministry of Health, Labour and Welfare. Moreover, since the area of medicine closely involves drugs and diagnostic equipment, the system must include information from private companies working in such areas. Thus, it is necessary to establish an information service organization based on linkages between industry, government and academia.

Personalized medicine is generally considered as an ideal form of medicine, but its implementation requires DNA for molecular diagnoses when using molecular-targeted anticancer drugs and participation of the public in translational research, i.e. demonstration research. Most of all, we must fully understand doctors' explanations when deciding on the therapeutic strategy for ourselves or our families. Thus, the rapid provision of high-quality information to the public is the most important task to secure public safety.

Glossary

*1 Pharmacogenomics
    The concept of analyzing the difference in drug response among individuals by utilizing human genome information and genome analysis techniques.

*2 Molecular-targeted anticancer drugs
    Anticancer drugs that are developed based on the molecular mechanism of cancer development and target the molecules responsible for cancer development.

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