4 Trust and the creation of biobanks

Biobanking in Japan and the UK

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Recent developments in biology and biomedical science have turned human beings into desirable research subjects. The revision to the Declaration of Helsinki in 2000 (WMA 2000) recognises the use of human material and data in medical research. Now, biomedical science has developed to the point that indirect medical research is partly replacing clinical research with living human subjects (HGC 2002; Masui 2002a, 2004a; NBAC 2001; NCBE 1995; Umeda *et al.* 1998). Moreover, economic interests in human health and disease augment this situation. Commercial enterprises are motivated to develop analytical agents, equipment, and information systems for indirect medical research. This situation is especially strengthened by the use of human genome information in biological studies of our species to stratify the human population into comparable and biologically standardised groups.

The indirect research methods using genome information, together with the use of biomarkers, medical records, and lifestyle data, are powerful strategies for understanding the human body and disease (HGC 2002; NBAC 2001; WMA 2000) and have increased the value of genetic material and data. For this reason, the establishment of biobanks (i.e. collections of genetic material and information) is a natural consequence of the developments in medical science.

However, many people are wary of the financial motivation of businesses involved in medical research, and this wariness could hamper participation in clinical studies. Since major operations such as large-scale biobanks require huge amounts of financial resources, and are under pressure to produce outcomes and return benefits, cooperation with commercial enterprises is necessary. Though commercial activity is regarded as the essential machinery of bridging a research outcome to a benefit for patients, commercial transfer of human information and material could cause intense scepticism among the public. The criticism and partial failure of the Icelandic Health Sector Database planned by deCODE Genetics, a commercial company, and the Icelandic state demonstrated difficulties in adjusting the interests and doubts among stakeholders (Annas 2000; Masui 2002b; Rose 2006).

People are more aware of their value to medical research, and they are increasingly conscious that their genetic material and data for medical research could be tightly bound to financial interests and commercial activities. Since genetic material contains individual genome information, which is both distinct and shared among human populations, and the stratification of human populations using genome information is critical for medical science, these two factors make genetic material sensitive.

Consequently, this chapter focuses on genomic research-oriented collections, such as biobanks, and some socio-political issues linked to such collections. I will also discuss the issues of benefit sharing, risk and benefit balancing, and trust and the motivation for donation. These issues will be examined in light of sustainable long-term policies by comparing biobanks in Japan and the UK. It will become clear that although Japan and the UK share problems, they solve them with different strategies, reflecting the diverging context of these countries.

The impact of developments in biology and biomedical science on medical research

The World Medical Association's (WMA) Declaration of Helsinki played an important role in the development of modern medical research. Human experiments during the Second World War made people aware of the need for appropriate guidelines on human experimentation. At the time, concerns focused on experimentation on the human body. The Nuremberg Code (1947) and the Declaration of Helsinki (1964) (WMA 2000) addressed these concerns. The Nuremberg code stands rigidly on the principle of consent; the Declaration tried to achieve practical adjustments. The Declaration follows the development of medical research, and the changes in the titles of the Declaration of Helsinki over the years clearly show that the targets of medical research have moved from individual patients to populations and from living human beings to genetic material and data (Table 4.1).

Table 4.1 Changes in the titles of the Declaration of Helsinki

1964:	'Clinical research on a human being'
	I. Introduction
	II. Clinical research combined with professional care
	III. Non-therapeutic clinical research
1975:	'Biomedical research involving human subjects'
	Introduction
	I. Basic principles
	II. Medical research with professional care (Clinical research)
	III. Non-therapeutic biomedical research involving human subjects (Non-clinical biomedical research)
2000:	'Medical research involving human subjects'
	A. Introduction
	B. Basic principles for all medical research
	C. Additional principles for medical research combined with medical care

In the 1964 version of the Declaration of Helsinki, the Declaration focused on traditional clinical research with physicians and individual patients. Here, scientific deduction was made on the basis of the accumulation of data from individual clinical cases. However, the 1975 version incorporated changes reflected in two instances of replacing vocabulary, i.e. from 'clinical' to 'biomedical' and from 'a human being' to 'human subjects'. These changes illustrate a development in biomedical science of an approach that emphasised the use of analytical technologies of the human body and diseases, that is, the biological view of the human body and diseases in medical research. For example, the biochemical analysis of blood with biomarkers represented an important advance in basic biochemistry and was soon widely used in a clinical setting. This advance pushed the development of modern medical practice based on a new scientific view of the human body and disease.

From the end of the 1980s to the 1990s, the Human Genome Project started slowly as an international collaboration. However, in 1998, the participation by Celera Genomics, a private company, threatened the status of the international collaboration. Around the same time, Iceland's parliament started to discuss legislation relating to the activities of deCODE Genetics, also a private company, in relation to the Icelandic biobank, and it passed the Icelandic Health Sector Database Act 1998. However, the planned project was unsuccessful, because the opt-out setting of participation and the right to withdraw the data had raised ethical and legal discussions. These incidents had a major impact on medical professionals and researchers and established a physical base or biological view of human beings.

The year 2000 Declaration of Helsinki, compared with the 1975 version ('Biomedical research involving human subjects') deleted 'Bio' from its title, changing it to 'Medical research involving human subjects'. The change illustrates that the majority of medical research is now based on a biological view of the human body and disease. In addition, the declaration defined *medical research* as involving 'identifiable human material and identifiable data'. The change in the definition meant that the WMA recognised the value of indirect methods of studying and measuring the human body and disease.

There might be also a political reason for the revision. In the 2000 term, Dr Eitaka Tsuboi, president of the Japanese Medical Association (JMA) at that time, was also the president of the WMA. A delegate from the JMA, who had joined the discussion, asserted during an interview that 'since so many non-medical researchers have come into the area of medical research using human material and data, the JMA and the WMA felt that it was our duty to protect the initiatives of medical doctors in medical research'.[1] As a matter of course, the medical doctor retains the initiative in clinical research involving human subjects. However, within the broad scope of 'indirect medical research methods', cooperation between medical doctors and other specialists has become a key issue.

Demand for biobanks

In the Declaration of Helsinki 2000 (WMA 2000), section four states that 'Medical progress is based on research, which ultimately must rest in part on experimentation involving human subjects'. Studies of the human body and disease are closely related to medical practice, and medical research is closely bound to the flow of money created by medical practice and care. The changes described in the previous section are related to the following two developments. On the one hand, the Human Genome Project paved the way for the construction of databases of the human body and disease, and made genome information the standard criterion for stratifying human populations. The availability of scientific criteria, i.e. genome information, transformed human beings into standardised and comparable subjects for medical research. On the other hand, studies of the human body and disease have become so closely intertwined with economic activities that the incentive for business to conduct medical research and participate in related activities has increased significantly. Both developments naturally require the collection of human material and information for indirect medical research in which non-medical research professionals from emerging research fields have their own identity.

This well-recognised environment for medical research means that human beings remain an attractive and appropriate subject for scientific studies. And biobank arrangements seem to function as bridging machinery used by medical doctors and non-medical researchers alike in biomedicine.

Biobank typologies

A biobank is a resource for indirect medical research on human health and disease. However, the term 'biobank' means something different depending on the context in which it is used. In this chapter, I prefer the superficial definition of biobank:

> A biobank is an organised collection of human material and information for medical study based on the optimal use of human genome information.

Biobanks can be private or public, commercial or non-profit based, large or small, etc. GeneWatchUK, a UK-based body monitoring research and policy issues of human genome research and genetically modified crops, defined biobanks as follows:

> Biobanks contain blood or cell samples from large numbers of people. Genetic information from each sample is linked to the individual's medical history and lifestyle data. There are already many small biobanks in the UK, and there are plans for a national biobank called UK Biobank. This would involve samples from 500,000 people and might be expanded later to include almost the whole UK population (GeneWatchUK 2006).

Any sample-based medical study can create biobanks. Within this broad category, however, we can classify biobanks by other criteria, i.e. target population, timeframe, and the health status of the population.

At the Organisation for Economic Co-operation and Development (OECD) meeting for 'Human Genetic Research Databases (HGRD): Issues of Privacy and Security' in Tokyo in February 2004, Dr Bartha Knoppers classified biobanks depending on the target population. There are basically four types: regional- or province-based biobanks, biobanks based on national populations, ethnic-based databases, and biobanks based on international/regional endeavours. Using a timeframe is another way of classifying biobanks. The biobank can be fixed at one point in time (cross-sectional), or it can include a follow-up research programme (longitudinal or cohort). Finally, biobanks can also focus on the health status of the target populations.

The OECD meeting used HGRD as an equivalent term for 'biobank'. The OECD report contains much information on the different types of biobanks in a global context (OECD 2006). In this chapter, however, I will discuss only the domestic issues of national biobanks.

Public and private biobanks

We can classify human resource banking systems into private and public ones. 'Public' here does not mean that the banking system is government-funded. Rather, 'public' refers to the function of biobanks in medical research. If a biobank distributes its collection to qualified researchers using an open and fair evaluation system, we call the biobank 'public'.

A 'private' biobanking system belongs to a specific organisation or person and supports specific researchers. Its biobanking policies govern the function of the organisation. The collection is not open to the public, and distribution of material and information is only for a collaborative or commercial purpose. Private biobanks can be supported by public funds. Alternatively, a publicly funded research project can create a private biobank, not open to qualified researchers.

During the OECD meeting in Tokyo, the following issues were discussed. When using genetic material and information, it is important for the biobank to be *public*, because (1) health data form part of a national heritage, (2) genetic data are essentially public and shared, (3) health data are recorded at public expense, and therefore, constitute a national resource, (4) it is essential that this resource remains open for public research, and (5) a public biobank avoids duplication of a collection. On the other hand, arguments for building a *private* biobank include: (1) health data are a commodity; (2) there is no inherent difference with traditional clinical trial data (data owned by the sponsor of clinical trials, data embodied in a drug master file for legislative purposes, and data exclusivity); (3) *de novo* collections require additional funds; and (4) the 'market place is always right' (OECD 2006). In addition it could be argued that a private biobank could serve the protection of sample donors well, as a private banking system could tightly control the use of human material and information. In practice, a public banking system would not be able to limit the use of data efficiently.

In the context of this discussion, even deCODE Genetics, which is a representative private biobank, was discussed in Iceland in a 'public' light:

> Due to the nature of the data and their origin, they cannot be subject to ownership in the usual sense, neither by institutions, companies nor individuals. It is, however, both fair and a duty to utilise the data in the interests of the health sciences and public health. This can best be done by the government authorising the creation and operation of a single centralised database, which has the following benefits: (1) acquisition of new knowledge of health or disease, (2) improved quality and economy in the health system, (3) development of high-technology industry and employment in Iceland, and (4) potential for attracting business to Iceland (OECD 2006).

Therefore, deCODE Genetics works under the guidance of the government and represents national benefits even though it initiated the commercial operation (Masui 2002b; Rose 2006). In this sense, the deCODE case is a quasi-public activity. This discussion clearly demonstrates the public nature of human genome material and data.

In any case, a biobank should maintain a public policy over data and sample collection. Another reason for public concern over biobanks lies in the way they are used and whom they benefit. It is important for the users of a biobank to maintain their public status and act accordingly. This leads us to the issue of the need for benefit sharing, though this discussion, as I will explain below, has great difficulty in resolving the problems of maintaining anonymity and the incompatibility of the benefactor and the beneficiary. To complicate the discussion on the nature of 'public' even further, it has to be pointed out that the concept has different implications depending on the context. This point will become clear when comparing the Japanese and British biobanks in the latter part of this chapter.

There is another reason for not regarding biobanking as a private commercial activity. Research resource banking systems require a large amount of 'dead stock'. Dead stock refers to potentially useful stock of data and/or materials that are not necessarily in constant use. This is important, for if a biobank collects only currently useful 'valuable' stock, the biobank would be out of date as research trends shift. Collections should not be too narrow and must be prepared for possible changes in the future. In this respect, the biobank does not fit the requirements of a private commercial activity, because a commercial activity seeks efficiency and does not tolerate 'dead stock'. This discussion raises issues of funding for biobank systems associated with their role in society.

Japanese genome research

In 2000, the Japanese government started the Millennium Project, a five-year target for science and technology in seven commercially promising areas (Government Office 2006). The project involved research on the human genome and required the creation of guidelines.

Coinciding with the planning of the Millennium Project in 1999, three cases of genome analysis were reported without the specific informed consent of the donors (METI 2006). And because genetic/genome information in Japan is regarded as the ultimate form of private information (Nukaga and Tsutani 2006), the mass media were eager to report misconduct in genome research. The three cases helped the government and academia to establish a consensus for the need of official guidelines on genomic research. The first ethical guidelines on genome analysis were issued on 28 April 2000 (MHLW 2006). The Ministry of Health, Labour and Welfare (MHLW) published 'the Millennium Guidelines'(*Idenshi Kaiseki Kenkyu ni fuzuisuru Rinrimondai tou ni taiou surutame no Rinrishishin*) for the regulation of millennium genome projects.

Independent of the guidelines, the Bioethics Committee, the Council for Science and Technology (BC, CST) (*Kagaku Gijutsu Kaigi, Seimei Rinri Iinkai*) issued the 'Fundamental Principles of Research on the Human Genome' (*Hito Genomu Kenkyu nikansuru Kihongensoku*) (CST 2000), on 14 June 2000. 'The Millennium Guidelines' were the standard operational protocol for researchers. The principles were influenced by 'the Universal Declaration on the Human Genome and Human Rights' of UNESCO 1997 (UNESCO 1997). These principles focused on a conceptual framework for genome research and were not intended as practical guidelines for researchers.

Other ministries have been funding human genome research projects, so the government decided to establish the guidelines in collaboration with three ministries: the MHLW, the Ministry of Education, Culture, Sports and Technology (MEXT), and the Ministry of Economy, Trade and Industry (METI). 'The Ethical Guidelines for Analytical Research on Human Genome/Genes' (*Hito Genomu/Idenshi Kaiseki Kenkyu ni kansuru Rinrishishin*) were issued on 29 March 2001 (MHLW, MEXT, METI 2001). The new guidelines replaced the old guidelines from the MHLW, merging the trends from the old guidelines, but covering a wider range and in some areas loosening the regulatory framework (issues of anonymity, surrogate decision-making process, and existing holdings).

From 2003, the Data Protection Bill (*Kojin Jyouhou Hogo Houan*) was discussed intensively, and the public became interested in the discussions regarding data protection. However, the use of genome information in research was not closely examined, which may have occurred because academic research was exempt from the Act (Article 50) and academic areas already had the guidelines. Of course, modifications to the guidelines were necessary according to the regulatory framework of the 2003 Act (*Kojin* 2003).

According to the Act, the MHLW drafted the 'Guidelines for Appropriate Handling of Personal Data in Medical and Care Services' (*Iryou/Kaigo kankei Jigousha ni okeru Kojinjouhou no Tekisetsu na Toriatsukai no tameni*), issued on 24 December 2004 (MHLW 2004). The guidelines established due process for data processing in medical practice and care. However, the guidelines provided very little information about how to transfer medical information from the medical field to research.

Since the Data Protection Act (*Kojin* 2003) became effective on 1 April 2005, the guidelines for medical research had to be adjusted to comply with the Act. The revision process was completed in December 2004, and became effective in April 2005 (MHLW, MEXT, METI 2004). The revisions focused on the area of data protection and the principles of safeguarding data, i.e. systematic, personnel, physical, and technical safeguards, and other adjustments according to OECD data protection principles (OECD 1980) that are incorporated into the Act (*Kojin* 2003).

The government also tightened the regulatory consistency between the explanations of the research purposes when obtaining informed consent from sample donors and the actual use of materials and information in medical research. As the new guidelines require the assurance of explicit consent, the range of research applications after informed consent is limited. These requirements in general are not suitable for biobank activities, because biobanks, in principle, serve future, still unknown research purposes.

Genomic research has generated several biobanks in Japan. I will describe two of them: the Pharma SNP Consortium,[2] and Biobank Japan.[3]

The Pharma Single Nucleotide Polymorphism Project

The Pharma SNP Consortium (PSC) was established in September 2000, and started its collection in February 2001, just before the three ministries jointly issued the guidelines for analytical research on human genome/genes (MHLW, MEXT, METI 2001). The Consortium gathered forty-three pharmaceutical companies, and collected samples from about 1200 'common' Japanese people. It collected the blood of donors, blood test results and data from questionnaires. The samples were completely anonymous and processed as unlinked data sets of DNA, blood, and sample information. The project was conducted at the Tokyo Women's Medical University, under the leadership of Professor Naoyuki Kamatani, and Professor Yusuke Nakamura's group of researchers at Riken[4] analysed the single nucleotide polymorphisms (SNPs). The project analyzed the frequency of SNPs of about 170 genes of drug-metabolising enzymes in a population of ordinary Japanese. The results are expected to serve as the normal control for pharmaceutical research projects.

The samples were donated with informed consent, but with two conditions: the permission for use by the PSC and the guaranteed donation of the samples to a public bank after the completion of PSC's project. The people who agreed to these two conditions participated as volunteers. The PSC processed the donated blood not only to purify the DNA for its own project, but also to make

immortalised cell lines by infecting the B-lymphocyte cell population of blood with the Epstein-Barr (EB) virus. Artificial infection of human B-lymphocyte with the EB virus causes an extended culture period or immortalisation without much alteration of individual genome integrity. Therefore, the EB virus transforms a limited resource from a donor to an almost unlimited resource of human DNA. After the completion of the project, the cell lines were donated to the Human Science Research Resource Bank,[5] and to the Japanese Collection of Research Biologicals, JCRB Cellbank.[6] These banks collaborate under the guidance of the MHLW.

Although this research plan received partial funding from the MHLW, it was initiated and primarily funded by consortium members of industry and was not part of the Millennium Project. In 2000, there were no specific guidelines applicable to the PSC genome project. Therefore, following publication of the Millennium Project Guidelines, the Consortium published its own guidelines.

This PSC genome project constitutes the first major collection of genome material for research by industry in Japan. As the collection of genome material and data was still a publicly sensitive matter, PSC maintained a cautious attitude during the whole period. The data was released in February 2004, and just after two months the data had been made accessible to the consortium members. As in other countries, the industrial initiative requires stricter standards than those of academia because journalists and the public watch their activities much more carefully than those of academics. The public policy was applied not only to the operation, but also to the collection of data, and the Consortium opens all its activities on its website. There may be other reasons for establishing public policy for PSC activities. It might be difficult to establish a consistent plan for the distribution of benefits among the members of the Consortium without it. Therefore, if a policy was devised for allocating certain periods of exclusive use of the data by members of the Consortium, the members would have to accept the policy of making the acquired data public. The other issue might be the continuation of funding. The generation of research data does not require much effort and funding after collection. On the other hand, the collected and immortalised materials demand care and back-up funding for long-term maintenance. The best use of publicly collected material might be considered as an ethical use of donated materials under the appropriate informed consent. This situation may have pushed the Consortium to establish its own public policy: all the established cell lines were donated to public cell banks. In this way, the collection became a useful tool in the public domain.

At the time of the donation of materials to the cell banks, the accompanying sample data from the cell lines remained at Tokyo Women's Medical University. In this way, the data and materials were managed independently, maintaining a high level of security. Professor Naoyuki Kamatani at the Women's Medical University was responsible for providing the available data upon request. The Consortium only lasted three years, from September 2000 to May 2003, but the collection has become a valuable public resource in Japan.

The data generated from the project is also accessible to the public. Those who wish to access PSC materials are asked to obtain authorisation for their project plans from their research ethics committee. This process is enforced because public policy stipulates the ethical justification for the use of donated materials and information. More importantly, donors were informed at the time of giving consent that a research ethics committee would authorise the future use of their materials from the public cell banks.

In the beginning, public biobanks discussed the international distribution of PSC materials. However, since many Japanese pharmaceutical companies are international, public biobanks decided to distribute the materials and information internationally as well as in Japan. In accordance with public policy lines, the PSC completely publicises its activities, protocols, proceedings of research ethics committees, research results, and materials and information. PSC, however, is an exceptional case in Japanese research, especially the 'public status' of the bank and its political transparency.

Biobank Japan

In the official Japanese papers, the concept of the 'biobank plan' appeared in a report from the Subcommittee on Science Project Evaluation and Life Science, Genome Research Working Party (*Genomu Kenkyu Ryouiki Shou-Iinkai*) on 20 March 2002.[7] The report included recommendations for a policy on genomic research in Japan. The report defined the 'biobank' as follows:

> a government supported collection of, preferably, immortalised and propagable EB virus transformed B-cell lines derived from patients and their family members, patients that have experienced adverse drug reactions, and volunteers. The collection should be voluntarily initiated and organized by researchers, medical doctors, and the pharmaceutical industry. The samples should be maintained and managed by the biobank and provided to qualified researchers upon request [translated by the author].

This description of the biobank reflects the practice of PSC described above. At this stage, the report recommended the collection of samples from 360,000 people, including 20,000 'normal' volunteers.

After the publication of the report, the Evaluation Subcommittee for Research Planning (*Kenkyu Keikaku Hyouka Bunkakai*), a subordinate of the Science, Technology and Academia Committee of the MEXT, issued the 'Promotion Strategy of Research and Development of Life Science' (MEXT 2002). In the report, the subcommittee recommended 'establishing the infrastructure for the management of resources and technology to realise personalised medicine (tailor-made medicine)' [translated by author]. On 24 July 2002, the Cabinet Committee of Science and Technology (*Sougou Kagaku Gijutsu Kaigi*) issued the 'Estimation of Science and Technology related Budget in 2003' (*Heisei 15 nendo no kagakugijutsu yosan no gaisanyoukyu ni*

mukete). The suggested budget was settled for the next fiscal year under the project title, 'The Realization of Tailor-made Medicine on the Genetic Characteristics of Individuals' (*Kojin no identokusei ni oujita teirameido iryou no jitsugen*), earmarking an estimated 40 billion yen (US$330 million) over five years (in a recent presentation, US$180million, October 2006). This plan became known as the Biobank Japan Project.

Biobank Japan aims to collect data from 300,000 patients (or cases) with over forty major diseases, in cooperation with over forty cooperating hospitals (Ohnishi and Nakamura 2005). This is primarily a five-year research project for collecting samples and information, with the supplementary function as a biobank. The study design includes the preparation of controls from the samples of patients with other diseases. The project defines the biobank as:

> A collection of DNA and serum of patients with certain diseases and patients with effectual and adverse drug reactions. Its infrastructure facilitates the analysis of SNPs and the creation of order-made ('made to order'; 'personalised') medicine [translated by the author].

The Biobank Japan Project started in the fiscal year of 2003 with the project title 'Realization of Order-made Medicine (*Ooda-ameido Iryou Jitsugen ka Purojekuto*)'.

Although the term 'order-made' is not English, its meaning is significant to the project. Professor Nakamura, its leader, favours the use of the term 'order-made', though the documents from the MEXT stick to the 'tailor-made' medicine. Professor Nakamura expressed his view that the concept of 'tailor-made' smacks of a class society, and said that genome science should provide benefits to the general public, not to a privileged elite. Therefore, if the research outcome only benefits the wealthy or is distributed along class lines, it would not be consistent with what Biobank Japan intends to offer the public. The spirit in which Biobank Japan was established, then, would have to be in agreement with the purpose of the public medical insurance system in Japan, which to a great extent has accomplished equality and solidarity with the financially underprivileged.

Biobank Japan is a large, case-control study and does not intend to perform follow-up studies. The project compares the genome–environment interactions of patients with a certain disease with those of carriers of another disease. For example, patients with diabetes might be studied in comparison with those with cancer. In addition, the secondary use of the collected material and information is part of the project plan. Biobank Japan announced that it provides collected material to qualified researchers, who have authorisation from the ethics committees of their institutes and meet the required qualifications of the biobank. However, Biobank Japan provides the DNA samples, but not the data, to the researcher. In the original plan, the research project which had received DNA material would provide the analytical results of the DNA to the biobank, and the data analysis centre of the biobank would analyse the DNA data with other medical and lifestyle data and return the final results. As I will describe below, the governance of material and information by Biobank Japan is very different from that of UK Biobank, which plans to provide data, but not distribute DNA material.

The British plan for genome research[8]

The UK House of Commons' Science and Technology Committee issued the key report 'Human Genetics: Science and Its Consequences' in 1995. This report provided the starting point for research policies on genome science and its application in the UK. Although, the committee criticised UK Biobank in its report 'The Work of the Medical Research Council [MRC]' in 2003 (House of Commons 2003), the 1995 report paved the way for the establishment of UK Biobank.

In 1998, two important events occurred in the field of genomic research. One was the participation of Celera Genomics in the human genome project, and the other was that the Icelandic parliament passed the Icelandic Health Sector Database Act. Although the Icelandic Health Sector Database was not successful for various reasons as I mentioned earlier, the Icelandic controversy stimulated discussion on the value of human genetic material and data.

In the planning process of UK Biobank, the MRC at the same time discussed a policy for the governance of materials and produced the interim guidance document 'Human Tissue and Biological Samples for Use in Research – Operational and Ethical Guidelines' 2001 (MRC 2001). An important point of these guidelines was to discuss the public status of human tissue collections and the governance of the funding body handling the collection.

UK Biobank

The author has been following the developments of UK Biobank from its inception (Masui 2002b, 2003, 2004b; Masui and Takada 2005). It is clear that UK Biobank cannot be regarded as a research project *per se*. Its aim is to collect biomaterials (blood and urine) and information (medical information, lifestyle questionnaires, and measurements) from 500,000 UK citizens, ranging in age from 40 to 69 years old, and to conduct a follow-up in 20–30 years.[9] Its aim is:

> UK Biobank project will enable scientists to gain a unique insight into the genetic and environmental causal factors associated with a wide range of debilitating diseases, providing vital information needed to work on future preventative and curative measures (Wellcome Trust 2006a).

The UK Biobank project is expected to provide research resources to qualified researchers. It is conceivable that the core concept of the UK Biobank project

is that of a social experiment set up to obtain the best possible outcome from human genome research in the context of the medical health sector in the UK. For this reason, UK Biobank serves as a custodian of the resources of UK citizens.

The UK started discussions on a population biomedical collection in late 1998. In May 1999, the MRC and Wellcome Trust (WT) held a workshop entitled 'UK Population Biomedical Collections', at which it reviewed major genome cohort projects funded by them. These funding bodies jointly announced that they would fund the preparatory steps of the UK Population Biomedical Collection in June 1999. In October and November of the same year, the WT held two consecutive meetings, the 'Workshop on Pharmacogenetics' and the 'Workshop on Human Biomedical Collections'. Moreover, in November 1999, the MRC issued the interim guidance entitled 'Human Tissue and Biological Samples for Use in Research'. These activities followed and strengthened the joint announcement in June. In the ethical guidelines, the MRC proposed a material governance policy and discussed public collection and custodianship because the fundamental question of a large biobank concerns its impact on not only individuals, but also society at large. For this reason, the MRC and the WT have maintained a policy of engagement in public debate on the public nature of the collection. These discussions focus in particular on the collection of UK Biobank and the National DNA banking network (Rawle 2003).

During the preparatory stage of UK Biobank, the MRC and the WT surveyed public perspectives on genome research and biobanks. They attached great value to obtaining public trust to facilitate progress in the biobank (PSP 2002). The acceptance rate for enrolment was estimated at around a quarter or less. It was therefore important for the success of UK Biobank that people in the locations for recruitment and in that particular age range were favourably aware of the aims and the process of the project. This meant that UK Biobank attached value to its public status and was motivated to survey the public perception of UK Biobank (PSP 2002). At the same time, they studied the perceptions of professionals in UK Biobank (Hapgood *et al.* 2006). Even though there was continuing criticism of the UK Biobank project (Giles 2006), the funding bodies and the biobank have come to feel confident and comfortable with its status.

In the spring of 2003, the funding bodies, consisting of the MRC, the WT, and the Department of Health, appointed a CEO and started practical moves for the project. UK Biobank was registered as a limited company and as a charity. In 2005, a new CEO was appointed. In my interview with Professor Rory Collins, the CEO of UK Biobank (February 2006), Professor Collins said that the project was planning to recruit people independently from general practitioners, and that UK Biobank had applied to the Patient Information Advisory Group (PIAG),[10] and obtained authorisation from the Minister of Health to survey potential participants without their consent. The terms of the PIAG are as follows:

> Section 60 of the Health and Social Care Act 2001 provides the power to ensure that identifiable patient information needed to support essential NHS activity can be used without the consent of patients. The power can only be used to support medical purposes that are in the interests of patients or the wider public, where consent is not a practicable alternative and where anonymous information will not suffice.[10]

In short, although UK Biobank itself does not have any specific legal powers, its activities are framed and supported by the Data Protection Act of 1998 and the Human Tissue Act of 2004.

Differences between Japanese and UK biobanks

As mentioned above, definitions of biobanks differ in a variety of respects. Although the biobanks in Japan and the UK are planned to be public, their different conceptualisations of public, risks, benefit, and trust affect their 'public' status. The scope of the differences reveals important points of consideration in the concept of collecting human material and information.

Preparing Biobank Japan and UK Biobank

The implementation of the plans for Biobank Japan started in the fiscal year of 2003. Until then, the Millennium genome studies (which had commenced in 2001) had experienced two years of practice, during which its guidelines had already been revised once in 2001 (MLHW, MEXT, METI 2001). The planning committee for the project believed that Japan was prepared for Biobank Japan, and that there would be no great need for further preparation (Ohnishi and Nakamura 2005). In fact, the project was believed to be a large and expensive version of the Millennium Project. The Japanese government did not regard this project as something new, so it had no notion of having to deal with the particular challenges of a social experiment.

The PSC project had been organised as an industrial initiative and had collected about 1200 blood samples from 'ordinary' Japanese people. It had immortalised the blood samples and donated them to the public banks. As described earlier, the success of the PSC project may have had a strong impact on Biobank Japan, because the practice of PSC had influenced the definition of 'biobank' used in the March 2002 report 'Genome Research Working Party' (*Genomu Kenkyu Ryouiki Shou-Iinkai*), chaired by Dr Yoshiyuki Sakaki. Biobank Japan established the Ethical, Legal, and Social Issues (ELSI) Working Group in 2003. And in 2004, the MEXT, the funder of the bank, established an ELSI Committee independently from the project.[11] Its task was to monitor and to advise the biobank project.

For UK Biobank, the draft of the Ethics and Governance Framework was open to public comments from September 2003, and public comments were summarised and published in May 2004. Then, the Ethics and Governance

Committee (EGC) first met in November 2004.[12] They discussed the issues of supervision and ethics and governance of UK Biobank. Preparatory activities for UK Biobank differed substantially from those of Biobank Japan, especially regarding the relationship between biobank and society. In 1995, the Science and Technology Committee of the House of Commons reported its views in 'Human Genetics: Science and its Consequences'. And in 1999, the Human Genetics Commission (HGC) was established to create long-term science and ethical policies on human genomic research.[13] Until the establishment of the Committee, there had been no initiative to create long-term policy recommendations. Since creating and implementing such a policy for genome research would require the cooperation of multiple ministerial departments, a central committee was regarded as indispensable.

In addition to this top-down infrastructure, the Department of Health and the Department of Trade and Industry decided to jointly fund the Genetics Knowledge Parks (GKP) for five years, from 2002 until 2007.[14] This created a bottom-up movement in the field. In 2004, the Human Tissue Act 2004 was passed,[15] and in 2005 the Human Tissue Authority was established to address the issues of human tissue,[16] the essential resource of genome information. This would provide the legal framework for the use of human tissue in genome research as a whole.

These elements of the policy of the House of Commons and the HGC, the engagement of GKP and the Ethics and Governance Committee (EGC, see below) and the legal framework, together with UK Biobank, give an edge to the UK in the area of human genome research. Moreover, these movements indicate that the UK government has seriously considered indirect human experimentation. This may be due partly to the UK tradition of epidemiology, which involves collecting medical data from UK citizens. The use of genome information is regarded as central to its future success. The UK policy, then, was a determination to build a robust trust based upon the dialogue between stakeholders. These activities were regarded as necessary for a mature society to consider and accept the possible outcomes of genome research.

Differences in the origin of researchers in UK and Japan

The academic background of researchers in biobank projects is an important factor in their development. In Japan, genetic research of single-gene disorders started in the 1980s. These studies were successful, and their outcomes created excitement among citizens and funding bodies. For this reason, genetic research based on DNA science has acquired a good reputation and much funding. The conclusion of the Human Genome Project changed the interests in genetics research from single-gene disorders to genome research of multifactorial diseases. In Japan, genetic researchers of DNA science who had been working on single-gene disorders were the first to move into the area of biobanks.

In comparison, in the UK, it was epidemiologists, by incorporating genome

information into their epidemiological analytical processes, who have led UK Biobank and existing genome epidemiology projects. Genome information would be a powerful tool in stratifying human populations, but the contribution of genetic factors is much smaller in common multifactorial diseases. Careful handling and examination of other human environmental information is essential to the study of multifactorial disorders of the human body. Epidemiology, which traditionally pursued the association of diseases with various biological and environmental factors, also provides methods for the study of multifactorial diseases.

The study of single-gene disorders has an exceptional position in the study of human diseases, focusing on the causative relationship between genetic information and disease. However, epidemiologists have struggled to obtain comparable data from multifactorial phenomena. In multifactorial research, a genomic factor does not necessarily constitute a major factor in causing a common disease. The study of the interaction between the genome and the environment requires skill in the collection of non-genomic information. In this sense, epidemiologists have an advantage in their academic training of collecting information on the human body in a comparative context.

Obtaining disease data is not without its complications, because individual doctors have different styles of diagnosis, and to study human disease requires standardisation of the description of each disease. Researchers then require standardised data on patients. Thus, data from blood tests seem suitable and useful, but they show only a one-time section of a patient and have limited value.

Therefore, obtaining human data may benefit from the experience of epidemiologists. Due to the difference in academic origins of biobanking in Japan and in the UK, then, the epistemological backgrounds of the biobanks in Japan and the UK are quite different.

Regulation of sampling

In Japan, clinical technicians draw most of the blood samples. However, a clinical technician can only draw blood up to 20 ml under a MHLW Notice.[17] PSC collected 30 ml (10 ml for biochemical analysis, 10 ml for DNA isolation, 10 ml for immortalisation of B-cell fraction), and Biobank Japan collects 20 ml (6 ml for biomedical analysis, 7 ml for DNA and plasma isolation, and 7 ml for serum isolation). The 20 ml limitation of the MHLW's Notice may seem to set a limit for sample collection.

There is another limiting factor in Japan. In ethical discussions, informed consent is of primary value in medical research planning. In Japan, the philosophy of informed consent strictly regulates the amount that can be sampled and the use to which it may be put. Consequently, medical researchers are very careful not to take 'unnecessary' or 'excess' blood when sampling. This trend may also limit the sample size.

Ten millilitres of blood yields about 200 μg of DNA. Thus, in Japan, the

immortalisation of samples is favoured because the immortalised cell line produces unlimited amounts of DNA samples from each individual. So the biobank report included an immortalisation plan.[18] However, the immortalisation process for blood is expensive and causes an increase in the chance of cross-contamination of samples. Therefore, the immortalisation of samples requires great care and a large budget.

As for sampling regulation in the UK, UK Biobank issued 'Sample handling and the storage, subgroup protocol and recommendations, version 1.0' on 7 July 2004 (UK Biobank 2004). It stated that the Biobank collects 40 ml blood (30 ml for DNA and plasma, 10 ml for serum). According to this sampling schedule, UK Biobank takes more than four times the samples for DNA analysis compared to Biobank Japan. Moreover, UK Biobank seems to be planning to save a limited amount of samples by conducting genome analysis within the biobank. In this way, they can recover leftover samples from the genome analysis. However, Biobank Japan has decided to provide a 5 μg aliquot of DNA and a 0.5 ml aliquot of serum from individual samples to a qualified researcher.[19] This illustrates a different strategy in governing samples.

On the distribution policy of data samples, UK Biobank plans to provide sample information to researchers, but Biobank Japan does not give the sample information to the researcher. In summary, the biobanks of Japan and the UK have greatly contrasting policies for governing genetic material and information.

Enrolment focus – differences in follow-up and risk management[20]

The UK Biobank project is a cohort study for up to thirty years, and enrolment will focus on 'ordinary' UK citizens. The bank follows the health status of participants during this period. The considerable follow-up process requires referencing and collecting samples and data from individuals. This requires long-term collaboration between researchers and participants. Although, in the original plan, the biobank itself does not perform the research, custodianship requires a well-prepared strategy and structure for supporting a dialogue among stakeholders in cooperation with the EGC.

In contrast, Biobank Japan aims to collect samples and information from patients, and perform research of their own, and does not include a follow-up programme. Patients are generally more amenable to research enrolment than volunteers. In the stage of research planning, one disease is compared to another disease as the control group. The collection schedule for Biobank Japan is of lower risk than that of UK Biobank because it does not contain long-term collaboration with research subjects and society.

The various scandals of the 1990s in the UK may have stimulated careful risk management of the biobank planning process. In particular, the public sector had lost credibility after scandals concerning BSE, GMO, and human tissue retention without appropriate consent. Programme officers from UK Biobank and the funding bodies were very careful about publicity, until the funding

bodies officially announced the establishment of the UK Biobank project in April 2001. Though the project requires enthusiastic participants, expectations that are too high may mislead people and result in the collapse of the project.

The idea was that 'too high of an expectation kills all'. Until they were ready to respond to the public or opponents, they wanted to keep UK Biobank low profile. Another aspect to the UK risk management strategy concerns the nature of the benefit of UK Biobank. The programme officers stated that the benefit of UK Biobank lies in the increase in knowledge. This basic statement is essential because it shows UK Biobank's intention to support competitive research projects without making any promises in principle. However, this is a difficult task.

If researchers only raise 'appropriate' expectations, they may not obtain sufficient support from the non-expert population, and funding bodies might lose interest in their projects. Therefore, researchers tend to exaggerate the promises of their research programme. Programme officers of UK Biobank, during my interviews with them, often complained about researchers who are promising too much. It is conceivable that the researchers felt that they should obtain the support of citizens and motivate funding bodies in the biobank project. This might be the cause for the behaviour of researchers during the incubation period of a research programme.

While transferring the knowledge on hypothetical and uncertain scientific research to non-experts, the possible failure of experimentation should be made explicit and discussed rationally and calmly. However, research results from studies in scientific communication revealed that the transfer of the hypothetical nature of science knowledge to non-scientists and even to scientists is not unproblematic (Shamos 1995).

Biobank Japan uses a very different risk management strategy. Biobank Japan operates in the name of the 'Realisation of "order-made" medicine', and it emphasises the practical benefits from the beginning. In Japan, among scientists there are many complaints about the poor acceptance of clinical research. There are various reasons for this, though the phenomenon is regarded as a reflection of a poor understanding of human experimentation. Next, it reflects the Japanese misunderstanding of science, i.e. science and technology are seen as the tamed servants for the well-being of humans. Emphasising the practical benefits of a research project is important for obtaining funds and the support of citizens, but this strategy increases the risks of a misunderstanding of the nature of science. In order to avoid the risks, the projects must guarantee substantial outcomes. It is said that this sequence of providing prospects beneficial to society is important in promoting research and it was praised in the third 'Science and Technology Basic Plan (*Kagaku Gijutsu Kihon Keikaku*)' of the Council for Science and Technology Policy.[21] However, this positive-reward cycle, i.e. positive outcome cultivates support of science, cannot absorb the uncertainty and hypothetical nature of scientific research, and might increase the risks associated with medical research and create a poor understanding of science.

Balancing risk and benefit

In medical practice, a patient and a doctor focus on the risks and benefits of a treatment to the patient. In the clinical setting, then, the subject is singular, and the focus is on the improvement of the condition of the patient, i.e. the well-being of the patient is the primary concern. By contrast, in the context of biomedical research involving human subjects, medical doctors and researchers cannot focus only on the benefits to a particular participant. The situation is described in the Declaration of Helsinki section 7, 'In current medical practice and in medical research, most prophylactic, diagnostic and therapeutic procedures involve risks and burdens'. Of course, the participant's welfare is the primary concern in research planning. Therefore, the Declaration states that: 'In medical research on human subjects, considerations related to the well-being of the human subject should take precedence over the interests of science and society (section 5)'. However, medical research is also concerned with the due course of scientific human experimentation. Since medical research needs to obtain scientific and comparable results, the experiments require randomised trials and placebos. The World Medical Association has spent much time discussing the 'placebo-controlled trial' and incorporated notes of paragraph 29 and 30 in the Declaration. Certainly, following due procedure places 'risks and burdens' on the participants.

Medical research of this kind therefore basically aims to bridge the participants' current risks and the burdens and benefits of the next generation. This idea is a central point of departure in medical experimentation. Thus, if we take into account the differences in medical research on living human beings and indirect medical research using genetic material and data, the latter could substantially reduce the risks and burdens of a participant in medical research experimentation. It is imperative that indirect medical research supported by biobanks is done as efficiently as possible so as to reduce the risks and burdens on human beings. In this sense, biobanks could have indispensable value to medical development and to the welfare of research participants and should be promoted.

Though benefits to the public are also an important issue for biobanks, the UK and Japan take the same stance of not paying the donors for participation. Since medical research produces benefits that are not meant for the participants themselves, but for the next generation, the donors expect that their tissues, cells, and information will contribute to the health of future generations. The policy requires the biobank to have public status and responsibility.

If we think of benefit sharing as a form of reciprocity, the ethical burden lies with the researcher's use of human material and data. As medical research may result in commercial benefit, academic honours, and public reputation, researchers should be aware of the public status of research resources. What it means in reality varies in each case. However, researchers must pay considerable attention to donors and society, as their cooperation enables them to study human beings and to perform indirect human experimentation.

No direct personal benefit to participants

Both the biobanks in Japan and the UK are careful to deny the personal gain, not only monetary but medical, of individual participants. The public has difficulties in accepting this.

In Japan, the idea of order-made or personalised medicine has been very popular, since it was thought that genome research would lead to a miracle cure for the diseases of individual patients. This idea seems to derive from the images of the workings of antibiotics against infectious agents. Or sometimes participants misunderstood how the genome research could benefit their own health. However, it takes a long time for research outcomes to produce a practical cure.

The idea was put forward that 'personalised medicine' resembles traditional medical practice focusing on individual patients; diagnostic and therapeutic information created by genome research of multifactorial diseases would not work differently from traditional medical knowledge in the essential sense. It was stressed that research results of population studies could be adapted to an individual patient at the clinical phase. In these aspects, medical research and treatment are different.

These ideas should be familiar to the general public. However, ordinary citizens do not see them in a favourable light, since direct and substantial benefit is easy to understand. Therefore, research domains should explain the consequences of medical research to make the participants and public understand them.

It is interesting that UK Biobank suffered a similar problem concerning the benefit to participants. In the public comments on the Ethics and Governance Framework 2003 (UK Biobank 2003), there were a few queries on what could be regarded as a substantial benefit to participants. As a policy, UK Biobank clearly denied the benefit to participants. The Ethics and Governance Committee, at the first meeting (November 2004), took the initiative in denying any substantial benefit or data return to participants and reconfirmed the voluntary status of the participants, so as not to raise unrealistic expectations (EGC 2006).

Although the biobank seems to be a natural consequence of post-sequence biomedical science in the genome era, we are not sufficiently prepared yet to accept this type of 'indirectly invasive' activity. Only if we build on the basis of trust can the idea of a biobank survive the many problems to come. Since the idea of research is not a promise in the future, in some cases 'unconditional' support should be necessary.

What is the role of trust in the participation in medical research?

In his memorial essay on human experimentation, the philosopher Hans Jonas claimed that in the course of medical research we should not depend on 'trust' because trust is not based on an equal relationship and on independence (Jonas

1974). Therefore, the trust relationship in principle cannot call for voluntary donations.

His claim is fundamentally important and correct, but I believe that in medical research it would not be practical and in some sense wrong. There are never entirely equal relationships between medical doctors or researchers and patients or participants in medical research. Medical research now involves non-medical researchers and often involves commercial interests. In practice, the researchers propose a research project to patients or healthy volunteers and try to obtain motivated participation. Of course, the motivation of the researcher not only focuses on the public good, but also on their personal and research interests. In the dialogue with research participants, the research domain encourages them with openness and a sense of responsibility to understand the intended results of the medical research project, which are intrinsically uncertain and can only be revealed in the (sometimes faraway) future. Without a responsible attitude, the participants cannot be encouraged to support medical research in the long run. If a project cheats its participants, medical research generally loses credibility and cannot build a trustworthy partnership between researchers and participants. Though the described process seems essential, a project needs to collect a certain number of participants within a certain period and cannot often tolerate the burden. The situation is painful, therefore, and the professionals in medical research should develop norms on medical research.

In this sense, the informed consent process of participants is important to researchers. This process gives researchers a chance to reflect on what they are doing with and to the participants. The process is indispensable in developing a norm for medical researchers. We should try and seek to establish professionalism in medical research. Professionalism is traditionally established in medical, legal, and religious areas. I believe that in the era of human experimentation we need to consider the issue seriously. In doing so, the words of Richard Shryock might be helpful to understand and make up our minds to take the nature of medical science of human diseases and its difference from 'science' *per se* (Shryock 1974).

> Physicians were the only scientists who, because they were also practitioners of a vital art, were constantly being pushed to hasty and careless conclusions. Other research men, uncertain in the face of new problems, could suspend judgment and proceed with due caution. Practitioners confronted with dying patients did not dare to wait; they must act quickly and, if necessary, 'take chance.' Even during hours stolen for research, they were still under pressure to get practical results *as soon as possible*.

Shyrock originally wrote this about 70 years ago, and the situation with current medical research does not seem to have changed much. We have to keep this in mind and maintain the dialogue between the various stakeholders and among

medical researchers and doctors. In this way, we can judge ourselves better in the coming era of human experimentation.

Reflections

Though the biobank projects discussed in this chapter may have differences, a minimum requirement for all biobanks should be the acquisition and maintenance of public trust. How can medical research, including genome research, build or acquire trust? Among policy-makers and related people, it is generally believed now that public engagement is essential. However, it is far from clear if public engagement is truly succeeding in engaging the public (Wellcome Trust 2006b).

To control the risks of genome research, scientists, medical doctors, and funding bodies should promote a dialogue with citizens to make them familiar with the uncertainties of science, rather than with exaggerated promises. However, it has been reported that the general public and even researchers, medical doctors, and policy-makers have a difficult time understanding the hypothetical nature of science. Moreover, we still have very few clues about the use of genome information-based research and biomedical research and the resulting medical practices.

Observations of the Japan and UK biobanks made me aware of the dynamism of dialogue among stakeholders. A philosophy of monitoring and compliance will never bring about an era of amenable human experimentation in research, since the system is essentially based on outside ruling that contrasts with the cultivation of voluntariness of research domain and public. If the system could build on benefit-exchange of the research and the participants, 'volunatriness' would not be necessary. However, it seems not easy to understand indirect and/or remote exchange of benefit. As discussed, medical research involved a huge amount of indirect connection or exchange among generations involving the research participants, benefactors, and the future patients and beneficiaries. Such a philosophy based on remote benefit will not motivate the public to participate in important medical research. And the trend to demand direct benefits of science and medical research will weaken and damage the trust in medical research, because most results of 'advanced' research, including genome research to date, have not been benefiting the present patients in practice. At this moment we have to 'believe' that we should cultivate the cooperation of motivated stakeholders and stimulate dialogue, and then we may be able to construct a system of supporting medical research. This process in itself could realise the best use of genome research based on the human material and information of individuals, such as biobanks can support. As a beginning, we need to strengthen our role and position in the indirect and remote processes involved in genome and medical research.

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Notes

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2 Available at: http://www.jpma.or.jp/psc/frame-j.html, in Japanese. http://www.jpma.or.jp/psc/frame-e.html, in English, last visited on 21 November 2006.
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4 Riken is a governmental institution of comprehensive research on science and technology. http://www.riken.jp/engn/r-world/riken_menu/index.html, last visited on 21 November 2006.
5 Available at: http://www.jhsf.or.jp/index_b.html, last visited on 21 November 2006.
6 Available at: http://cellbank.nibio.go.jp/cellbank.html, last visited on 21 November 2006.
7 The Subcommittee on Science Project Evaluation and Life Science, Genome Research Working Party (*Genomu Kenkyu Ryouiki Shou-Iinkai*) was chaired by Dr Yoshiyuki Sakaki. It is located under the Committee of Science and Technology, and Academia (*Kagaku Gijutsu Gakujutsu Shingikai*) of the MEXT.
8 For a thorough review of the regulatory frameworks of Japanese and British genome research, see Porter, P. (2004) 'The regulation of human genetic databases in Japan', SCRIPT-ed http://www.law.ed.ac.uk/ahrb/script-ed/issue3/japan.pdf). He made an extensive comparison between the Japanese guidelines (2001 version) and the Ethics and Governance Framework of UK Biobank. The Japanese genome research guidelines have been revised, though the basic framework has not changed.
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