THE ETHICAL AND LEGAL FRAMEWORK SURROUNDING BIOBANKS AND MOLECULAR EPIDEMIOLOGY IN JAPAN

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1 Governmental Ethical Guidelines for Biomedical Research in Japan

1.1 Several Sets of Guidelines for Biomedical Research

Since the fall of 1999, Japanese government ministries have promulgated many sets of ethical guidelines for biomedical research.

Recent increase of governmental ethical guidelines began with the drafting of the "Guidelines on Ethical Issues Surrounding Genome Analysis Research" by the Ministry of Health and Welfare (MHW) in April 2000. In October 1999, MHW announced a large 5 year human genome analysis research project (Millennium Genome Project) as a part of governmentally funded Millennium Project which was to start in April 2000. MHW, recognizing the ethical and social problems involved in the genome research, prepared this set of guidelines that was to apply only to genomic research conducted under the Millennium Genome Project. This set of guidelines is often called as "Millennium Guidelines."

As the Millennium Guidelines were not applicable to genome researches outside of the Millennium project, the ministries concerned with genomic and genetic research embarked on the task of drafting of a common set of genome research guidelines in the summer of 2000. This effort produced Ethics Guidelines for Human Genome/Gene Analysis Research in March 2001 (hereinafter cited as "Genome Guidelines").

Besides Genome Guidelines, governmental ethical guidelines promulgated so far include Guidelines for Derivation and Utilization of Human Embryonic Stem Cells (September 2001); Guidelines for Handling of Specified Embryos (December 2001); Ethical Guidelines for Epidemiological Research (June 2002); Ethical Guidelines for Clinical Research (July 2003); Guidelines for Clinical Study of Gene Therapy (March 2002. The original gene therapy guidelines were enacted in June 1994).

The common features of these guidelines are the requirements of voluntarily given informed consent, protection of personal information, review and approval by research ethics committees that is composed of members of multiple disciplines and of both sexes.

1.2 Revision of Guidelines in 2004

Many of the guidelines were revised at the end of 2004 to make them compatible with the requirements of the Personal Information Protection legislation that had been enacted in May 2003 and would take full effect in April 2005. Although the legislation explicitly exempts researchers of academic institutions from specific obligations regarding personal information processing for the purpose of academic research, most obligations thus exempted have been incorporated in the guidelines revised in December 2004.

1.3 Biobank and Genome Guidelines

As biobanks and researchers who use their specimens are supposed to make genome/gene analysis research, the Genome Guidelines govern their operation and researches.

Genomic/genetic information, which is unique to each individual, will not change for life, and may indicate the future onset of or susceptibility to particular diseases. These characteristics of genomic/genetic information justify an individual's control of it and special protection against the violation of its confidentiality.

1.3.1 Requirement of informed consent

The Genome Guidelines provide the requirement of voluntary informed consent and participant's right to revoke his/her consents anytime (but before total anonymization of specimens and data) without any disadvantages.

Guideline 10(3) provides that before receiving a specimen and clinical data from a donor, the principal investigator must obtain a written consent based on his/her free will (informed consent), after providing him/her with an adequate explanation of such matters as the significance, objectives, methods and expected results of the research, disadvantages that he/she might suffer, and the method of preservation and use of a human specimen and clinical data. Guideline 10(9) provides that the donor or his/her proxy may withdraw at any time in writing his/her informed consent without suffering any disadvantage.

1.3.2 Protection of Personal Information through Security Measures and Anonymization

Guideline 6(3) provides that the head of research institution must take the organizationally, personally, physically and technologically effective measures to secure the protection of personal information processed by it, including the measures for the prevention of its leakage, loss and destruction.

The Guidelines make it a rule to anonymize specimens and data before they are used in research. Guidelines 14(2) further provide that where the specimens are deposited to a human cell/gene/tissue bank, the principle investigator depositing them must ensure that they will be anonymized in an unlinkable manner when distributed to researchers and abide by the conditions stipulated by the donor or his/her proxy.

2 Biobank Japan and J-MICC Study

2.1 Personalized Medicine Project and Biobank Japan

A five year governmentally funded $180 million project led by Professor Yusuke Nakamura of the Institute of Medical Science of the University of Tokyo, was launched in the spring of 2003[1]. The project, named "Personalized Medicine Project," was first conceived as a research and development project to revitalize the Japanese economy, and, in a sense, is a successor to the Millennium Genome Project. It has four major aims, that is (1) discovery of genes susceptible to diseases, or those related to efficacy or adverse reactions of drugs; (2) providing the useful information of molecular target for evidence-based development of drugs or diagnostic methods; (3) providing the important

medical information that can be applied for establishment of "Personalized Medicine"; (4) genetic and environmental epidemiology for prevention of diseases. The methods used to realize these goals are (1) Collection of DNAs, sera, and clinical information from 300,000 patients of 46 listed diseases in 2003 - 2007; (2) Construction of Biobank Japan (DNAs are stored at 4 degree Celsius and sera at -150 degree Celsius in N_2) that provides samples to the researchers in academic and private institutes in Japan; (3) systematic genomics (mainly SNP analysis) and proteomics analysis; (4) Identification of genes of medical importance.

2.1.1 Informed Consent Procedure by Medical Coordinators

The patients of the listed diseases are offered opportunities to hear the explanation concerning the cooperation with the project. The invitation is extended from the attending physician at the end of seeing a patient. The recruiting of the patient is being done only at the hospitals of 12 collaborating medical institutions. When the patient accepts the offer, he/she will meet a medical coordinator of the project. Medical coordinators are personnel (usually medical staff such as nurses, laboratory technicians, etc.) specially trained to give the patient information regarding the involvement in the project and obtain the patient's consent on behalf of the project head. In the process of informed consent, it is emphasized that the patient's consent must be perfectly voluntary, the patient is under no obligation to cooperate with the project, he/she would suffer no harm if he/she declines to be involved, and no personal benefit, therapeutic or otherwise, will accrue from the participation. Even where the patient has given consent to be involved, he/she will be assured of the right to revoke his/her consent any time without incurring any disadvantages or liabilities. Where the patient gives consent to the medical coordinator, 2 syringes of 7 cc of blood (one for DNA extraction and the other for serum separation; blood for DNA extraction is taken once and blood for serum separation will be taken once a year if the patient returns to the hospital) will be taken and medical data recorded.

2.1.2 Anonymization of Specimens and Data

The subject's specimen and clinical data are sent to the clinical databases located in the collaborating institutions. There each specimen, set of clinical data, and the subject's personal information will be given a common code number (2 dimensional bar-code is used). When syringes of blood are sent to clinical laboratories for serum separation and DNA extraction and tubes of resultant serum and DNA are deposited in the Biobank, the subject's personal information does not accompany. Similarly, when the subject's clinical data are gathered in the combined clinical database, they are without personal information. The subject's personal information will never go out of the clinical database of each collaborating medical institution, and, in the Biobank, combined clinical database and data management laboratory, specimens and data are identified only by the 2D bar-code. Further, when the specimens are distributed to the research institutes, they will be given once again randomly assigned numbers.

2.2 J-MICC study

Japan Multi-Institutional Collaborative Cohort (J-MICC) Study consists of about 10 semi-independent research projects now in the process of planned by researchers of universities and medical institutes. They are connected by the common aim of investigating the associations of disease risks with lifestyle, genotypes, and biomarkers. Led by Professor Nobuyuki Hamajima of Nagoya University School of Medicine, the

project plans to collect blood, lifestyle information and medical data of a total of 100,000 people. The subjects are to be aged 35 to 69 years and residing in the defined areas. They will be recruited from the inhabitants of specified areas, health checkup examinees, and patients of a cancer hospital.

2.2.1 Protection of Subjects

The principal means of protection of subjects are, like the Personalized Medicine Project, requirement of informed consent and protection of personal data through anonymization of specimens and information at the local institutions where they are collected. When specimens and information arrive at the J-MICC central office, they are identified only by the 2D bar-code.

2.2.2 Follow-up Investigation of Protection of Privacy

As this study is a longitudinal cohort study, the researchers plan to follow the participants for 20 years with regard to their death and diagnosis of cancer. The means utilized for the follow-up include the resident registration data kept by the local administrative office, death certificate data, cancer registry data, and the information obtained from the replies entered in the second or additional survey sheet. When diagnosis of cancer is learnt through the resident registration, second or additional survey, it is planned that inquiry will be made at the hospital where the diagnosis is made in order to verify it and obtain the accurate information surrounding the diagnosis. Legally, this will amount to the disclosure of the subject's information by the hospital to the third parties (researchers) that is in principle prohibited without the subject's consent. Following the recommendation of a research ethics committed reviewing the project, the project plans to clear the requirement by obtaining the subject's consent two times, i.e. once when informed consent is obtained initially to the participation in the study and for the second time shortly before the hospital inquiry is undertaken.

3 Experiences as a Member of Ethics Committees

I am now a chair of both the ELSI Committee of the Personalized Medicine Project and the Committee for Social Affairs of the J-MICC study. I will describe the experiences gained as a committee member.

3.1 ELSI Committee of the Personalized Medicine Project

Soon after the project started in the spring of 2003, the ELSI Working Group was established under the Project's Steering Committed (Working Group's first meeting was held in August 2003). However, because it was not independent of the Steering Committee and lacked its own secretary office, it could not work efficiently and was replaced by the ELSI committee in September 2004. Although the ELSI Committee still does not have its own staff (its secretarial work is done by the officers of Ministry of Education, Culture, Sport, Science and Technology (MEXT)), standing, at least formally, on the equal footing as the Steering Committee, it can now perform its duty more efficiently and flexibly.

The committee now consists of 9 members (a medical scientist, a sociologist, a journalist, a genetic counselor, two representatives of patient groups, a bioethicist, a practicing lawyer, and a law teacher. 4 of them are female and 5 are male. A university professor and

former MEXT officer was its 10th member before his resignation in July 2005 on his appointment as a senior officer in the secretarial office of Science Council of Japan) and meets once a month. Its activities includes (1) visiting collaborating hospitals to make on-site checking of the informed consent procedures and personal information protection system; (2) inspection of the records of the research ethics committees of the participating institutions regarding the ethical review of this project; (3) checking the project's system for distributing specimens to outside researchers; (4) ensuring the project's conformity to the revised Genome Guidelines.

In July 2005, the ELSI committee submitted the report covering its activities during the fiscal year 2004. We concluded that by and large the project had been carried out properly from the ELSI standpoint without any serious problems.

At the same time, we indicated several points that we thought should be improved. Firstly, with respect to the protection of personal privacy of the prospective subjects, there exists a wide variation among the collaborating hospitals in the environments in which the informed consent procedure is conducted. At one hospital, two or more potential subjects were never admitted in a coordinator's room at once for the informed consent procedure. At the other hospitals, prospective subjects shared the same table which is separated only by a partition on it and could hear the conversation of others easily. Secondly, we proposed that the project provide information to the subjects and collaborating hospitals by such means as newsletters in order to keep up their interests and promote their cooperation. Thirdly, with respect to the knowledge of medical coordinator, it is suggested that they should be provided with more training in the field of intellectual properties so that they can explain about them more confidently (I personally feels that even when the coordinators are very knowledgeable about intellectual properties, explaining them to lay persons is quite challenging task). Fourthly, it is suspected that medical coordinators who enter clinical information into database do not sufficiently understand the significances of each entry to accommodate to different ways of recording the medically same data.

3.2 Committee for Social Affairs of the J-MICC study

The Committee for Social Affairs of the J-MICC study started its activities in June 2005. Now, we are reviewing the protocols of the J-MICC study and those of the individual study by the participating study group. As the J-MICC study group consists of about 10 semi-independent research projects to be conducted by researchers, who are affiliated with separate universities and institutes, it was found that embodying the J-MICC study and individually conducted study in one protocol is sometimes not easy. We had the impression that the information sheet to be given to the prospective subjects are also complicating. Like the ELSI Committee, we are planning to make site visits to check the informed consent process and protection of personal information.

3.3 Personal Experiences [2]

Lastly, I will write a few comments on some of the problems experienced during my involvement in the ELSI aspects of the two projects.

First question is concerned with the subjects' ability to understand the genomic research and biobank. As biomedical technologies continues to advance with accelerating speed, it is suspected that some, or perhaps, most prospective participants might not really understand the full significance of the subject to which their consent is requested.

Secondly, it is pointed out that researchers might not be able to project the every detail of their study plan (e.g. what part or what kind of genome to investigate, whom to join as a

co-researcher or which commercial laboratory to entrust the work of extracting the DNA) that is necessary for them to provide the specific image of the research to the prospective subjects.

Thirdly, the difficulty of striking an ideal balance between ensuring the voluntariness of subjects and efficient implementation of the research often troubles me. For instance, with respect to the J-MICC study, a research ethics committee directed the project to insert on the front page of lifestyle investigation sheet the phrase that you don't have to answer the question that you don't like to answer. Of course, insertion of this phrase is desirable from the standpoint of ensuring the voluntariness. However it is feared that it might detract from the seriousness and integrity of the answer.

Fourthly, in spite of the rule that personally useful information, if found as a result of research, is not to be sent back directly to participants, it still seems that some of the subjects and clinical researchers tend to expect it.

Lastly, the ways control samples should be collected from and their explanation given to participants seem a challenging question. However we must grope for the proper treatment.

I would like to stress that although the first three problems above are theoretically difficult, they can be solved rather easily in practice if researchers could won the trust of the citizens. If the citizens trust researchers, the research projects (including biobanks) release freely the information on the developments of their program and the subject are assured of their right to retract their consent any time, I am rather confident that they rarely invoke to the right.

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[1] The early phase of Biobank Japan project was introduced in R. Triendl. Japan launches controversial Biobank project. Nature Medicine. 9(8): 982, 2003. See also, A. Mandavilli. Profile, Yusuke Nakamura. Nature Medicine 10(6): 560, 2004.

[2] See generally, K. Maschke. Navigating an ethical patchwork--human gene banks. Nature Biotechnology 23(5): 539-545, 2005.