The Regulation of Human Genetic Databases in Japan

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Methodology

This report presents the current regulatory framework for human biobanks in Japan as it has been set out in two recent sets of guidelines; the 'Fundamental Principles of Research on the Human Genome', created by the Bioethics Committee of the Council for Science and Technology in Japan in June, 2000; and the 'Ethical Guidelines for Analytical Research on the Human Genome/Genes', issued on March 29th 2001 by the Japanese Ministry of Health, Labour and Welfare, the Ministry of Education, Culture, Sports and Technology and the Ministry of Economy, Trade and Industry. Where appropriate, these Guidelines are contrasted and compared with the proposed UK Biobank Ethics and Governance Framework, and points of convergence and significant differences between the Japanese and British approaches are highlighted.

In addition to close textual analysis of these Guidelines, illustrations from Japanese civil law, as well as excerpts from Japanese primary legislation and from published secondary materials have also been included in this report. An attempt has been made to critically present the main streams of thought in the Japanese academic literature, and to draw out possible weaknesses or areas of uncertainty within the Japanese approach, as well as its strengths. Where Japanese language materials have been used, the standard procedure of producing a phonetic translation of the Japanese in roman lettering, followed by a translation into English has been followed. Whilst every effort has been made to ensure the accuracy of Japanese-English translations, the author accepts full responsibility for any changes in nuance which may have occurred.

Executive Summary

Regulators drafting the legal and ethical framework of the UK Biobank Project are attempting to achieve a complex and delicate balance of interests. The regulatory structure which they devise must maximise the usefulness of the Biobank as a long-term resource for a variety of population-based genetic studies. At the same time, regulators must also strive to protect the rights and dignity of the donors of genetic material on whose highly-sensitive information this research will be based. When weighing the various competing interests, it may be useful to observe the ways in which other jurisdictions have attempted to regulate human genetic databases- to analyse the successes and problems of their regulatory frameworks and see how behaviour has evolved in those countries in practice. Viewed in this spirit, Japan may prove to be a valuable and informative case study in the regulation of human biobanks.

In both Japan and the United Kingdom, the state-sponsored development of the bioinformatics sector has increased the need for public trust and support for medical research, and in both Japan and the U.K., this has come at a time when public faith in the medical and research communities is at a particularly low point following a series of high-profile medical scandals. Further factors have raised significant additional challenges for the drafters of the Japanese guidelines, giving them perhaps an even more arduous task than that of their British counterparts. Privacy concerns amongst the Japanese general public are perhaps even more acute than in the UK, due to hypersensitivity about potential genetic discrimination and the general aversion in Japanese society to discussing the issues raised by inheritable disease. Western

(primarily American) concepts of bioethics have been introduced into Japan only relatively recently, and while some medical professionals have actively sought to reduce paternalistic attitudes and to integrate more patient-centred decision making into their clinical practice, leading Japanese bioethicists have nevertheless been critical of the current rather limited reception of bioethical principles amongst the Japanese medical and research community. The perception in the eyes of the Japanese public of a medical research community which is reluctant to change in spite of widespread pressure serves only to further entrench the current atmosphere of mistrust. Some observers have suggested that the combination of these factors will likely serve to discourage public participation in biobank projects in Japan.[1]

In order to demonstrate some credible mechanism for protecting the rights of research subjects and win back a degree of public trust, two sets of guidelines have recently been introduced in Japan to regulate the collection, utilisation and storage of human genetic material: the 'Fundamental Principles of Research on the Human Genome', created by the Bioethics Committee of the Council for Science and Technology, which was published in Japan in June, 2000[2]*; and the 'Ethical Guidelines for Analytical Research on the Human Genome/Genes', issued on March 29th 2001 by the Japanese Ministry of Health, Labour and Welfare, the Ministry of Education, Culture, Sports and Technology and the Ministry of Economy, Trade and Industry.*[3] *Both sets of Guidelines aim to achieve public understanding and to develop a secure and fair environment for genetic research. The two major themes which run through both sets of Guidelines are autonomy and privacy; these have been articulated in the forms of informed consent and anonymisation respectively.*

However, despite providing fairly detailed guidance with regards to the duty to obtain full informed consent and to protect the privacy of research participants, some Japanese commentators have pointed out that a number of issues have not been entirely resolved by the two sets of guidelines. Firstly, it has been suggested that the current guidelines grant too much power to individual Ethics Review Committees, and fail to set clear limits on the exercise of their discretion.[4] *Secondly, the current guidelines have also been criticised for not giving sufficient attention to the issue of the precise circumstances under which samples may be linked to research subjects and correlated with medical records, environmental data and other personal information which could potentially be used to identify a particular individual, and the conditions under which such sensitive data may be transferred to external organisations or subcontractors.*[5] *Thirdly, some observers have pointed to the fact that these guidelines are not hard law but gyosei shido (administrative guidance) - a commonly-used Japanese administrative technique which is often favoured in fast-moving areas such as biotechnology, where formal legal regulation is frequently perceived to be too restrictive.*[6] *Although the Ministry of Health does back its*

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[1] "Data Security is Crucial for Japanese Science" (2002) Nature, Vol. 417, p.689.

[2] *Available on-line at* http://www.ruhr-uni-bochum.de/kbe/gensokue.pdf (last visited September 1st, 2004).

[3] *Available on-line at* http://zobell.biol.tsukuba.ac.jp/~macer/eghgr.htm (last visited September 1st, 2004).

[4] "Japan Guidelines Under Fire After Protest Halts Study" (2003) Science Vol. 301, p.1039.

[5] Masui, T. and Takada, Y., "Ethical, legal and social issues of genomic research- New phase of genome research desperately requires social understanding and safeguards on the use of medical records and other personal information" (2003) Yakugaku Zasshi 123 (3) 107-119. (*Japanese only*).

[6] *See generally*, Oda, H., *Japanese Law*, (1999), *Butterworths*.

guidelines with the threat of sanctions such as the withdrawal of research funds from institutions which violate its provisions, it is unclear what normative impact the guidelines will have on private research institutes which are not dependent on state funding.

At a broader social level, the regulatory culture surrounding biomedical issues in Japan has also been criticised, as the current lack of public debate and discussion about advances in human genetics is seen by some as being symptomatic of an overly paternalistic culture towards decision-making and policy in the medical sphere. Many observers have suggested that there is an urgent need for more public engagement with regards to biobanks and their benefits in order to win public support and understanding. The UK Biobank project has been cited in Japanese academia as being laudable in this respect.[7]

Nevertheless, the UK Biobank and similar projects such as Generation Scotland can perhaps learn from some elements of the Japanese regulatory framework. Particularly interesting features of the Japanese regime are the control mechanisms of the requirement of detailed research protocols which must be approved by the Ethics Review Committee before research can proceed, and the institutionalisation of the interaction between individual researchers, head researchers and Ethics Review Committees. Furthermore, the designation of dedicated information protection managers in Japan to anonymise samples and to ensure participants' privacy by storing biological samples separately from medical records and other information which could potentially identify participants, and the rules for withdrawal of consent (both by the individual concerned and their representatives) are also noteworthy aspects of the Japanese regulatory approach. One significant divergence from the UK Biobank regulatory framework is a Japanese participant's right to know his or her genetic information, where this is technically feasible, with provisions made for genetic counselling where this is appropriate. Discussions are still continuing on the issue of when and how to provide health information to participants in the UK Biobank. Finally, the example presented in this report of Kyushu University's commitment to benefit sharing with participants may help to overcome some of the current negative publicity surrounding medical research in Japan, and give credence and credibility to the Fundamental Principles' stated objectives of making a genuine contribution to the health and welfare of participants and to society as a whole.

1. Regulating Biobanks in Japan

1.1 Current Biobank Activity in Japan

The Japanese Government has identified the growth and development of its biotechnology industry as being vital to ensuring Japan's continued economic prosperity in the 21st Century. Biotechnology's privileged status prompted the Japanese Government to initiate its *"Basic Strategy Towards the Creation of Biotechnology Industry"* in 1999, which provides substantial funding to a number of projects designed to enhance both the international competitiveness of Japan's biotech sector and to apply scientific advances to bring benefits to the health and welfare of

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[7] *See* Masui, T. "Eikoku baiobanku keikaku no imi suru mono (*The Meaning of the UK Biobank project*)" (2003) Jurist, No.1247 pp.29-36. (*Japanese only*).

the Japanese population.[8] The '*Basic Strategy*' is coordinated by five ministries and agencies, including the Science and Technology Agency, the Ministry of Agriculture, Forestry and Fisheries, and the Ministry of International Trade and Industry. Through sizeable investment in strategic areas, the programme aims to create 1000 Japanese biotechnology companies and a market worth 25 million yen (approximately 118 billion GBP) by the year 2010.[9] In the post-genome-sequencing era, it appears that the advancement of Japanese technical capabilities in the area of *bioinformatics* has been assigned a particularly high priority. The various ministries aim to consolidate existing genetic analysis projects and use them as the foundation for further 'post genome' informatics research. Much of the current wave of bioinformatics work focuses on research into *Single Nucleotide Polymorphisms* (SNPs)- variations of a single nucleotide believed to be the cause of most phenotypical variations from hair colour to disease susceptibility.[10] Researchers believe that mapping SNPs will assist in the understanding and analysis of human disease and drug response. As the racial background of the Japanese is relatively homogeneous and as some SNPs which are prevalent in the Japanese population are not commonly found amongst Caucasians, it is consequently believed in Japan that the investigation of "Japanese SNPs" should be pursued as a discrete unit of study.[11]

1.2 The "Millennium Projects"

As part of this overarching strategy, the biotechnology-related component of the Japanese Government's *'Millennium Projects'*-a five-year plan targeting areas of science and technology with high economic potential- aims to provide financial investment to create a multitude of new SNP databanks and to consolidate and incorporate a number of earlier bioinformatics and database projects (which were initiated in the pre-genome-sequencing era of the late 1980's and early 1990's) into larger databases.[12] Of the new databases being assembled, the BioBank Japan Project and the Japanese contribution to the International HapMap Project are perhaps the best known, but a number of smaller studies administered under the auspices of the Millennium Projects also promise to further knowledge significantly in the field of human genomics.

1.3 The BioBank Japan Project

With obvious similarities to the UK Biobank, the large-scale BioBank Japan Project is designed to study sets of 'high-value' SNP markers against genetic samples from

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[8] Stuart, C., "Human Genetic Databases in Japan", UK Parliament Select Committee on Science and Technology, Memorandum by the Science and Technology Section of the British Embassy, Tokyo, (2000). *Also see* "Japan Pushes to Capitalize on Biotechnology" Nature Biotechnology (1999) 17, 320 - 321 (01 Apr 1999); "Japan Banks on Budget to Boost Biotechnology" Nature Biotechnology (2000) 18, 142.

[9], "Japan aims to launch 1,000 biotech companies in 10 years" (1999) Nature Vol. 397.

[10] *See* Japanese Pharma SNP Consortium homepage, http://www.psc.gr.jp/ (last visited September 1st 2004).

[11] *Id.*

[12] Early Japanese database projects include GenomeNet, the Kyoto Encyclopaedia of Genes and Genomes (KEGG), Laboratory of Genome Database, the DNA Databank of Japan (DDBJ), KDRI-DB and the Kazusa DNA Research Institute. *See* Stuart, *supra* note 8.

approximately 300,000 Japanese individuals over a five-year period.[13] The project commenced in April 2000 as a collaboration between the Human Genome Centre (HGC)[14] at the Institute of Medical Sciences, Tokyo University (IMST)[15] and the Japan Science and Technology Agency (JST). The project's objective is to identify up to 150,000 SNPs prevalent throughout the human genome within two years and to develop analytical tools for research into genetic polymorphisms. The BioBank Japan Project team is being led by Dr. Yusuke Nakamura, director of IMST's Human Genome Centre and group director of the Research Group for Personalized Medicine at the RIKEN Genome Science Centre.[16] Dr. Nakamura is also the principal investigator for Japan on the International HapMap Project.

1.4 The International HapMap Project

The International HapMap Project is a worldwide initiative intended to create a map of common patterns of SNPs.[17] The Project is a collaboration between scientists in the U.S National Institutes of Health (NIH), the RIKEN Genomic Sciences Centre in Japan, and research institutes in the U.K., Canada, China and Nigeria.[18] The Project officially started with a meeting on October 27-29, 2002, and is expected to be completed within around three years.[19] The goal of the initiative is to analyse human SNPs in an effort to identify *haplotypes*, or sets of associated SNP alleles in a region of a chromosome, that can be utilised to further understanding of human disease.[20]

1.5 Other BioBank Projects and Initiatives

In addition to the high-profile Japan Biobank project and the Japanese contribution to the International HapMap, there are a large number of other state-sponsored bioinformatics and biobank projects currently in operation at an estimated 40-50 research institutions. Other Millennium Projects include various SNPs databases to conduct research into specific diseases, such as cancer[21], dementia[22], high blood

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[13] "Japan launches controversial Biobank project"*Nature Medicine* (2003) 9, 982. Further information about the Biobank Japan project can be found at http://snp.ims.u-tokyo.ac.jp/(last visited September 1st 2004).

[14] Located within the Institute of Medical Science at the University of Tokyo, the Human Genome Centre (HGC) was completed in 1991. The HGC contains 8 laboratories, and was the leading institution during Japan's contribution to the Human Genome Project. http://www.hgc.ims.u-tokyo.ac.jp/(last visited September 1st 2004).

[15] The Institute of Medical Sciences, Tokyo University (IMST). http://imswww.hgc.jp/imswww/indexe.html (last visited September 1st 2004).

[16] The RIKEN Genome Science Centre was completed in October 1999, *See* the Riken Genome Science Centre (GSC), http://www.gsc.riken.go.jp/ (last visited September 1st 2004).

[17] *See* http://www.hapmap.org/index.html.en (last visited September 1st 2004).

[18] Riken SNP Research Centre, http://www.src.riken.go.jp/indexE.html (last visited September 1st 2004).

[19] *See* http://genome.gov/10005336, (last visited September 1st 2004).

[20] *Supra* note 17.

[21] Databases are also being constructed at the National Cancer Research Institute (NCCRI), IMSUT, the Japanese Foundation for Cancer Research, Japan Medical College, Kyushu University, Osaka University, Kumamoto University, Tohoku University; Tokyo Institute of Technology, Molecular Cell Biology Institute of Tokyo University. *See* Stuart, *supra* note 8.

[22] National Centre of Neurology and Psychiatry (NCNP), MHW Tokyo University, Niigata University.

pressure[23], asthma/allergy[24] and diabetes[25]. Major national databases include many that were established in the pre-genome era of the 1990's, including GenomeNet[26], the Protein Research Foundation,[27]the DNA Databank of Japan[28], the Kazusa cDNA[29] database, RIKEN's new Human Organised Whole Genome Database 'HOWDY' [30]and the Japanese Collection of Research Bioresources (JCRB).[31]

Another recent observable trend is the increasing input of the private sector in genomic research projects. The "Pharma SNPs Consortium" (PSC) was set up in September 2000 to investigate the role that specific SNPs play in the onset of common genetic diseases and conditions and to apply the knowledge gained to the design of tailor-made pharmaceuticals with reduced side-effects.[32] Forty-three Japanese pharmaceutical companies will participate in the project, and will collect blood samples from a target number of 1,200 volunteers. Research themes include: the location of single nucleotide polymorphisms in a pharmacokinetics-related gene; the frequency of SNP emergence in the general Japanese population, and; the analysis of the expression and function of the mutation-type protein generated under the influence of SNPs. A database will be built to accommodate research results and after the filing of patents, the data will be open to the public. The research period will be for three years with a total investment of 1 billion Yen (approximately 5 million pounds). Professor Nakamura of IMST (above) has been appointed as Director of the project.[33]

A further category of databases are the "private collections" among researchers of universities and medical research institutes who have been pooling samples while undertaking research programmes funded by Monbusho and the Ministry of Health

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[23] National Cardiovascular Centre Research Institue, MHW Ashikawa Medical College, Ehime University, Tsukuba University.

[24] National Children's Medical Research Centre (NCMRC), MHW Tsukuba University, Juntendo Medical College, IMSUT.

[25] Research Institute of the International Medical Centre of Japan, MHW Gunma University, Chiba University, Kobe University, Tokushima University.

[26] http://www.genome.ad.jp/ (last visited September 1st 2004). GenomeNet is a Japanese network of database and computational services for genome research and related research areas in molecular and cellular biology. GenomeNet was established in September 1991 under the Human Genome Program of the then Ministry of Education, Science and Culture (Monbusho).

[27] http://www.prf.or.jp/en/(last visited September 1st 2004). The Protein Research Foundation funds the Protein Research Institute in Osaka University and holds Japan's major peptide sequence database.

[28] http://www.ddbj.nig.ac.jp/intro-e.html (last visited September 1st 2004).. DDBJ (DNA Data Bank of Japan) began DNA data bank activities in earnest in 1986 at the National Institute of Genetics (NIG) with the endorsement of the Ministry of Education, Science, Sport and Culture.

[29] *See* http://www.kazusa.or.jp/huge/ (last visited September 1st 2004).

[30] *See* http://gdb.jst.go.jp/HOWDY/ (last visited September 1st 2004).

[31] http://cellbank.nihs.go.jp/(last visited September 1st 2004). The JCRB consists of a number of cell and gene banks operated by the National Institute of Health Sciences (NIHS) and the National Institute of Infectious Disease (NIID) respectively. Both Institutes are administered by the Ministry of Health and Welfare (MHW).

[32] *See* Japanese Pharma SNP Consortium homepage, *supra* note 10.

[33] *Supra* note 10.

and Welfare (MHW). As a general rule, these institutions tend not to share their samples beyond their groups or institutes.[34]

1.6 The Final Goal- Towards a Comprehensive Database?

Stuart observes that in the coming years, the final goal of the Millennium Projects seems to be to consolidate the information contained within the 'first generation' databases and collections of cells, tissues and genes, and to integrate these data (as well as that obtained by current biobank projects), into a single, 'comprehensive database'. However, it appears that at the current time there is no universally clear idea amongst those involved as to the exact motives for developing such a database or as to the precise applications to which it would be put.[35]

1.7 Fostering Public Trust and Encouraging Participation

In Japan, as elsewhere, the success of these and subsequent biobank projects depends not only on the quality of the science and technology to be applied in genetic analysis, but also upon the ability to secure *public participation*- an issue which in turn hinges upon engendering *public trust*. When viewed from this perspective, Japan's current push into bioinformatics development comes at something of an inopportune moment for the Japanese Government, as trust in the medical profession is at an historic all-time low.[36] A number of high profile medical scandals have severely undermined public faith in the ethical integrity of the once-highly respected medical establishment, which is now generally perceived by the Japanese public as being 'unable to regulate itself'.[37]

A further important factor which may discourage biobank participation in Japan is the fear of genetic discrimination in the context of marriage, employment and insurance. This anxiety is highly accentuated in Japan, where hereditary disease has traditionally been stigmatised and even discussion of hereditary disease is generally shunned.[38] In the last few years, incidents of medical institutions selling patient's medical information (complete with full medical history, address and telephone number) to pharmaceutical companies and pharmacies have not helped engender public trust with regards the way the medical profession protects confidential information.[39] The Japanese Medical Association has issued repeated warnings that this particular attitude towards genetic disease in Japan, combined with the current mistrust with which Japanese medical and research professionals are regarded, is likely to result in a general reluctance to participate in genetic research programmes, particularly if a

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[34] *See* Stuart, *supra* note 8.

[35] *Id.*

[36] *Supra* note 1.

[37] "Doctors Far from Malpractice Accountability" The Japan Times: March 22, 1999; "Japan: Convictions in *Blood* Scandal" Associated Press, 24 February 2000.

[38] *See* Stuart, *supra* note 8.

[39] See "Iryo joho no denshika to puraibashi sanko" (*Considerations on the digitalisation of medical records and privacy*), (Japanese only); *Also see, the Sale of name lists and medical records,* the Asahi Shinbun (Asahi Newspaper) 30th Nov. 1999.

credible and secure system of personal data protection cannot be demonstrated to the Japanese public.[40]

1.8 The Japanese Regulatory Framework for Human Biobanks

In order to bring much needed harmonisation and uniformity to this patchwork of ethical standards, two sets of guidelines have recently been introduced in Japan to regulate the collection, utilisation and storage of human genetic material: the '*Fundamental Principles of Research on the Human Genome*' (the *Fundamental Principles)*, created by the Bioethics Committee of the Council for Science and Technology in Japan in June, 2000; and the '*Ethical Guidelines for Analytical Research on the Human Genome/Genes*' (the *Ethical Guidelines)*, issued on March 29th 2001 by the Japanese Ministry of Health, Labour and Welfare, the Ministry of Education, Culture, Sports and Technology and the Ministry of Economy, Trade and Industry. Both sets of Guidelines aim to achieve public understanding and to develop a secure and fair environment for genetic research.[41] Both the *Fundamental Principles* and the *Ethical Guidelines* bear a degree of similarity to the broad principles outlined in the UNESCO Declaration on the Human Genome and Human Rights.[42]

Two major themes which run through both sets of Guidelines are *autonomy* and *privacy*, which have been articulated in the forms of *informed consent* and *anonymisation.* The most salient points shared by the guidelines are:

i. The use of informed consent forms to mediate almost all aspects of the relationship between researchers and research subjects;

ii. The consultation at all stages between research subjects and individual researchers or research groups, the head of research institutions and Ethics Review Committees. Research must proceed upon the authorisation of the Ethics Review Committee and the permission of the heads of the research institute. Ongoing progress reports regarding the research, as well as its results, must be reported to the Ethics Committee;

iii. The decision as to whether or not to participate in a programme of research should not result in any difference in terms of therapeutic treatment for an individual, and consent may be withdrawn with no prejudicial effects towards the subject during such time period as withdrawal is possible;

iv. Measures for the anonymisation and protection of personal data must be implemented;

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[40] *Supra* note 26.

[41] The *Ethical Guidelines* state that "it is desired that research on the human genome/genes be conducted with the understanding of society thus obtained. In Japan, however, rules that facilitate such social understanding have not been adequately established and it is therefore an urgent issue to set forth concrete guidelines for the proper conduct of research activities on the human genome/genes in general with full respect for human dignity and the human rights of participants and their blood relatives or families. It has been an **urgent issue** to establish precepts for the proper conduct of analytical research on the human genome/ genes with respect for human dignity and rights with social understanding and public support. *Ethical Guidelines*, p.3 [author's emphasis].

[42] UNESCO Universal Declaration on the Human Genome and Human Rights**,** 11 November 1997, *available on-line at*; http://portal.unesco.org/en/ev.php-URL_ID=13177&URL_DO=DO_TOPIC&URL_SECTION=201.html.

v. The donation of biological materials is voluntary and without financial reward. Furthermore, intellectual property rights and other economic benefits which may arise as a result of the research will not be attributed to the participant.

Although the Guidelines set the parameters for further information collection, they are not retrospective. The Guidelines are not intended to apply to clinical laboratory tests designed to obtain genetic information for direct therapeutic benefits to the subject or his/her blood relatives. Nevertheless, it is stipulated that such tests and analyses of the human genome should be properly conducted with due respect for the aims of the present Guidelines and with reference to other guidelines established by relevant organisations.

2. Understandings and Consent

2.1 Recruitment

Participation in Japanese Biobanks and genome research will be entirely voluntary, and the collection of blood and tissue samples etc. for research purposes may only proceed once the participant has given his or her informed consent.[43] This notion of voluntary participation is further reinforced by Section 1 Principle 5 ("*Basic Conditions*") of the *Fundamental Principles*, which states that "[a]n individual who is requested to provide a research sample but does not consent to that request should not be disadvantaged as a result of his/her refusal."[44]

The selection process itself must be fair and rational, and the reason why a candidate is being invited to take part in a genome research project should be disclosed to both the prospective participant and the Ethics Review Committee overseeing the research project.[45] If a candidate for participation has or is suspected to have a disease or a medical abnormality such as an abnormal drug response, the candidate should be informed of the name of the disease or be given an equivalent description of the abnormality.[46] At the current time it is still unclear whether or not genetic researchers in Japan will attempt to enlist suitable research participants through coordination and collaboration with general practitioners.

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[43] *Fundamental Principles*, Principle 5 (1), "*Basic Conditions*".

[44] The Japanese guidelines thus take the same approach as the proposed *Ethics and Governance Framework* of the UK Biobank, which also states that "[p]articipation in UK Biobank will be voluntary" Version 1.0 (For Comment), 24 September 2003, (I) Relationship with participants, (A) Recruitment, (1) General Principles, p.7.

[45] *Ethical Guidelines*, Chapter 3 (*Basic Attitude to Participants*), (8) (*Informed Consent*),(1), "The chief researcher should not select candidates for participants in an irrational, unjust or unfair manner".

[46] *Ethical Guidelines*, Chapter 3 (*Basic Attitude to Participants*), (8) (*Informed Consent*), Bylaw regarding informed consent of participants with a disease or a particular health condition.

2.2 The Reception of the Doctrine of Informed Consent in Japan

Despite Japan being a signatory to the 1964 Helsinki Declaration[47] and a number of other international instruments, the integration of the concept of respect for patient autonomy, with informed consent as its primary expression, has been a slow and gradual affair.[48] It appears that as a normative matter, there remains significant diversity with regards to the degree of importance attached to the doctrine amongst members of the medical community. More traditional and conservative institutions have shown little enthusiasm for change from more paternalistic approaches to patient care.

Nevertheless, in recent years, a number of rulings from the Supreme Court have finally established informed consent *as a legal matter* within Japanese medical jurisprudence. In a 1981 ruling, the Japanese Supreme Court stated that physicians have a legal duty to explain the nature and the risks involved with the surgery which is to be carried out, and can only proceed once consent has been obtained.[49] A further significant legal development occurred in a 2000 Supreme Court ruling, where damages were awarded purely for mental suffering as a result of the breach of the duty to obtain informed consent (and with no claim with regards physical harm) in a case where a doctor performed a blood transfusion on a patient despite her autonomous decision not to undergo the transfusion due to her religious beliefs.[50] Nevertheless, some observers suggest that the doctrine is still at an early stage of its reception. Rihito's criticisms of the limited understanding of informed consent would suggest that the acknowledgement of informed consent as a legal matter in Japan has not necessarily been uniformly translated into behavioural change or normative consensus with regards to the degree of significance that should be attached to the doctrine in a clinical setting. [51] However, this situation is perhaps likely to change in

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[47] The World Medical Association Declaration of Helsinki, "Ethical Principles for Medical Research Involving Human Subjects," adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and substantially amended on areas such as informed consent by the 29th WMA General Assembly, Tokyo, Japan, October 1975; 35th WMA General Assembly, Venice, Italy, October 1983; 41st WMA General Assembly, Hong Kong, September 1989; 48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996 and the 52nd WMA General Assembly, Edinburgh, Scotland, October 2000. Note of Clarification on Paragraph 29 added by the WMA General Assembly, Washington 2002.

[48] See Waseda Biolaw homepage, http://www.human.waseda.ac.jp/jinsoken/projects/bios.html. (last visited September 1st 2004).

[49] Supreme Court of Japan, Showa 56 (1981), 6, 19 Ruling, No. 1011, Section 54.

[50] Supreme Court Ruling, Heisei 12 (2000), 2, 29, Civil Collection No. 54 Section 82 Ruling No. 1710 Section 97. Tejima, Y, *Considerations Regarding the Calculation of Awards of Damages for Violation of the Duty to Inform as Part of Consent in Medical Treatment*, (2001) Jurist, No. 1199. Other Supreme Court rulings which discuss the duty to inform include the Supreme Court Showa 61 (1986), 5 30 ruling No. 1196 section 109 (physicians are not under a duty to inform patients about the medical institution where they are being transferred to), and in relation to notification of a diagnosis of cancer; the ruling of the Supreme Court in Heisei 7 (1995), 4, 25 Civil Collection section 49 No. 4 section 2263 is generally understood to be the first case which actually affirmed the liability of medical professionals to pay damages.

[51] Kimura, R. "Images of Health and the Traditional Medicine - Bioethical Perspectives" Japanese Journal of Acupuncture 47 (3), 1997, pp. 93-100 available on-line at http://www.bioethics.jp/lichtthesis97_9-j.html (Japanese only). Rihito Kimura, Professor of Bioethics and Law at Waseda University, is perhaps Japan's most fervent advocate of bioethics, and has criticised the limited understanding of informed

light of the aforementioned Supreme Court rulings, perhaps more for defensive legal reasons than because of unanimous agreement amongst the Japanese medical and medical research community on the normative and ethical significance of respecting patient autonomy.

This ambivalence with regards to informed consent has been even more apparent in the conduct of *ex-vivo* medical research, with a number of incidents demonstrating what appears to be the complete lack of any kinds of ethical controls or respect for individual autonomy when gathering blood and tissue samples. For example, in 2000, researchers at the National Cardiovascular Centre in Osaka, the University of Kyushu, Fukuoka, and Tohoku University, Sendai, all admitted that they had used thousands of blood samples for analysis without obtaining prior informed consent from patients.[52] Events such as these received considerable attention in the Japanese media, further compounded public mistrust and fuelled the perception that the Japanese medical and scientific community has little regard for patient/subject rights, and is generally "unable to govern itself".[53] A particular fear amongst Japanese researchers is that without a credible legal framework for the protection of subject's interests, a lack of support from the Japanese public will force Japanese scientists to gather their samples and conduct research in other countries where coherent legal controls have ensured willing public participation.[54] At least one leading Japanese geneticist has complained of difficulties in obtaining tissue samples for research due to the scarcity of willing donors.[55]

The two sets of guidelines therefore come as a move to construct a framework which will enable scientists to conduct effective research while simultaneously protecting the rights of research subjects. Both sets of guidelines give extensive details with regard to the types of consent needed before DNA samples may be obtained and genomic analysis can be undertaken.

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consent in Japan. In this paper, Prof. Rihito suggests that the current conceptualisation of informed consent in Japan, which consists of an explanation of the treatment by the physician, which is then followed by the consent of the patient, does not meet with the ideal of informed consent, as physicians will typically fail to provide adequate information regarding alternative courses of treatment, and their various advantages and disadvantages. Rihito states that "[a]s most people are aware, the term 'informed consent' means that when a diagnosis (and a course of treatment is decided) is made, the details of that diagnosis must be accurately transmitted to the patient. First of all, let us consider whether in Japan the information is being accurately conveyed. In present-day Japan a change has occurred with regards informed consent. However, there are still many cases where the details of the diagnosis are not conveyed, for example in the case of patients with cancer. Furthermore, it is essential that in accordance with the details of the diagnosis, what steps will have to be taken, the risks and success rate and the prognosis must also be conveyed to the patient. Mere explanation is also not sufficient. Informed consent means that the explanation must be easily understandable and presented in a way which will enable the patient to comprehend and feel satisfied with the course of treatment" (*author's translation*).

[52] "Japan set to tighten ethics rules for genetic sampling" (2000) Nature 403, 819-820.

[53] *Supra* note 1.

[54] *Id.*

[55] *Supra* note 52.

2.3 Defining Informed Consent in the Context of Genomic Research

The central importance of informed consent in the context of genomic research is enshrined in Chapter 2, Section 1 (*Informed Consent*), Principle 5 "*Basic Conditions*" of the *Fundamental Principles*, which states that:

> *"A research sample may be collected from an individual subject for research on the human genome only after the participant has first been given a sufficient explanation of the research, and has given, of his/her own free will, his/her informed consent…..The consent should be expressed in writing".*[56]

The *Ethical Guidelines* define *informed consent* in the following way:

> *"The consent voluntarily given for provision and handling of samples etc. by research subjects who are requested to provide them after having been explained in detail beforehand by the chief researcher about the significance, objectives and methods of planned research, anticipated outcomes and inconveniences and other relevant information and having fully understood such details. The present Guidelines require that informed consent be obtained in writing".*[57]

This definition of informed consent can be deconstructed to reveal the following three component elements:

i. **A duty to explain:** When the researcher is obtaining informed consent, the objectives, methods and potential outcomes of the research, and also any disadvantages and losses that the participant might incur should be explained in a clear and understandable way.[58]

ii. **A duty to ensure that the patient has understood the explanation:** The person who explains the proposed research to the participant, for the purpose of obtaining their informed consent, **should be careful that the participant fully understands the experiments** in which his/her sample will be used, and the significance of the act of providing the material.[59] When obtaining consent researchers should take into account the fact that participants do not always have a good knowledge of research on the human genome. For this reason, explanations should be given in several steps, each time confirming that the participant has understood up to that point. An explanation using written material, for example, is desirable because it can give the participants as much time as they need before they make a decision to consent, and can indicate particular points for reflection.[60]

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[56] *Supra* note 43.

[57] *Ethical Guidelines for Analytical Research on the Human Genome/Genes* (Japan), Chapter 6, *Definition of Terms*, (8) *Informed Consent*.

[58] *Fundamental Principles*, Chapter 2 (*Rights of participants*), Section 1, (*Informed consent*), Principle 5 (Basic Conditions).

[59] *Fundamental Principles*, Principle 7, (*Diversity of research*).

[60] *Fundamental Principles,* Section 1 (*Informed Consent*), Principle 5 (*Basic Conditions*).

iii. **A duty to obtain informed consent in writing:** The consent should be given in writing and a suitable record kept. However, if a participant has difficulty or is unable to consent in writing for a particular reason, such as difficulty in writing or motor functions, appropriate alternative methods, e.g. audio-visual recording, should be prepared. Alternative methods should be chosen in place of written consent only if there is such an impediment for the participant, and not for the sake of convenience for the researchers.[61]

A detailed explanation of the issues that must be specifically included in the informed consent form can be found in the *Ethical Guidelines'* "*Bylaw regarding the contents of the written information for informed consent*", which is attached in *Appendix I*. The proposed contents of the consent form for participants in the UK Biobank are attached as a point of comparison in *Appendix II*.

2.4 The Scope of Consent & 'Comprehensive Consent'

A recurrent problem with the use of the doctrine of informed consent in biobank projects is that often at the time that consent is given, it is not (nor cannot be) totally clear precisely what the subject is consenting to. This is particularly an issue in Japan, where it is anticipated that the same biological samples may be utilised in a number of genome analysis studies or integrated within larger databases. As a general principle, when participants grant consent they are consenting to the researcher carrying out research specifically within the framework of the particular research project that has been explained and outlined to them. Nevertheless, due to the value of samples to researchers, the *Fundamental Principles* permit a significant softening of the strictness of this requirement by permitting researchers to obtain *'comprehensive consent'*; where consent is granted not only to a specific and defined project, but to which the consent granted extends to other genome analysis or to other related medical research. Typically this will mean that the subject will consent to the use of their samples in a specific and defined research project, and also that they consent to the use of their samples for '*studies aimed at other purposes*'.[62] The requirements for obtaining comprehensive consent are further elaborated in Principle 8 1.(*b*) of the Fundamental Principles, which provides that:

> *"In this case, sufficient information, which clearly outlines the anticipated objectives of the research at that point in time, should be given to the participant so that s/he can thoroughly understand the significance and consequences of the fact that the sample provided will be used in "studies aimed at other purposes…"*[63]

In accordance with the general principle of obtaining informed consent outlined in the previous section (2.3), detailed information should be given about *other genome analyses and related medical research that are anticipated at that time,* regardless of

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[61] *Id.*

[62] *Fundamental Principles*, Principle 8 (1), (a), "If a participant consents to provide a research sample for genome analysis in a particular research project and, at the same time, anticipates and consents to the use of the same sample in other genome analyses or related medical research, then the research sample may be used for the latter "studies aimed at other purposes."

[63] *Fundamental Principles*, Principle 8 (1), (b).

whether any of them are actually undertaken later. Nevertheless, the explanatory notes go on to stress that "comprehensive consent *should not be solicited simply for the sake of convenience or saving of labour*." The control mechanism at this stage is the Ethics Review Committee, which must approve the research protocol and the type of informed consent to be obtained. The temptation to obtain comprehensive consent as a way to gain a free hand to use research samples can thus only be tempered by an Ethics Review Committee. In any event, a research project requiring comprehensive consent should not be approved by an Ethics Review Committee unless the confidentiality of the personal information of the participant (including genetic information and identifying information) is guaranteed.[64] It is also reiterated in Principle 8 paragraph 1.(c) of the *Fundamental Principles* that protocols pertaining to the management and protection, including anonymity, of genetic and other personal information of the participant should be explained in detail, and that strict confidentiality should be guaranteed.

2.5 The (Re-)Use of Existing Samples

The issue of whether samples which were obtained before the two sets of Guidelines came into force can be re-used in new genomic studies has also been addressed. Principle 9 of the *Fundamental Principles* establishes a general prohibition on the use of existing samples (obtained before the coming into force of the *Fundamental Principles* i.e. June 14th, 2000) in new genetic research projects. Under the strictest interpretation of Principle 9, such samples "should be destroyed immediately", along with any research results exclusively deriving from them.[65] However, the subsequent section of Principle 9 then goes on to detail in fairly broad terms the circumstances under which researchers may derogate from these guiding principles.[66] The *Ethical Guidelines* provide more detail and divide existing samples, such as tissues cells, body fluids and excretions, and the DNA extracted from them, into three categories (group *A*, *B* & *C* samples) with regards the scope of the consent under which they were obtained and the criteria that must be satisfied before they can be re-used in new projects of genome and genetic analysis.

Group A Samples Samples, etc. for which consent was given for use in research including the human genome and gene analysis when they were provided.	**May be used** in research on the human genome/ genes within the scope of the original consent.
Group B Samples Samples, etc. for which consent was given only for use in research not explicitly including the human	**Should not in principle be used** in research on the human genome/ genes unless informed consent is newly obtained from the participants or their representatives etc. or procedures are taken to anonymise the

64 *Id.*

65 *Ethical Guidelines*, *Bylaw regarding destruction of samples.*

66 *Fundamental Principles*, Principle 9 (*Existing samples*).

genome and gene analysis (e.g. consent given for "use in medical research") when they were provided.	sample (the sample is anonymised and permission) and authorisation for usage is given by a research committee.
Group C Samples: Samples etc. for which consent was not given for "use in medical research" when they were provided.	**Should not in principle be used** in research on the human genome/ genes unless informed consent is newly obtained from the participants or their representatives etc. concerned in accordance with the procedure and method as stipulated in the present Guidelines or the sample is anonymised and submitted to an ethics committee "for a more broadly considered decision on whether or not the use of the sample is reasonable."[67]

Principle 9(3) of the *Fundamental Principles* gives some guidance as to how Ethics Review Committees should evaluate requests from researchers to authorise the reuse of *group A, B, or C* samples in new genetic studies, stating that:

> *"…if the research to be undertaken requires the use of an existing sample for which informed consent was not obtained at the time of provision, or if the research to be undertaken is beyond the scope of the consent obtained, the said sample should not be used prior to the proposed research undergoing a review by the Ethics Committee. The Ethics Committee should determine the conditions for the use of existing samples, including requirements for re-obtaining informed consent, taking the following points into consideration: the anonymity of the sample, the possibility of linking the sample to the donor, the nature of the sample, the research plan and details of the said research, the potential impact on the participant, et cetera, and measures for the protection of personal information."*[68]

The issue of the scope of informed consent was a significant point of contention in the discussions on the *UK Biobank Ethics and Governance Framework*. Opinion was divided on the question of whether the Biobank could legitimately adopt a pragmatic approach whereby *broad consent* (i.e. *consent to participate in UK Biobank with all that that implies*[69]) would be obtained, enabling the Biobank to then utilise the sample in a wide-range of genetic studies, or whether under the strictest interpretation of the principle of autonomy underpinning the Helsinki Declaration, it would be necessary to obtain *specific consent* from participants for each and every research project making use of their samples and data in order for the consent to be valid and for the Biobank project to be ethically acceptable.[70] Most commentators on the 2003 *UK*

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[67] Stuart, *supra* note 8.

[68] *Fundamental Principles*, Principle 9(3).

[69] UK Biobank Ethics and Governance Framework, Background Document, Prepared by the Interim Advisory Group on Ethics and Governance, 10 October 2003.

[70] *See* The UK Biobank, Ethics Consultation Workshop, 25 April 2002.

Biobank Ethics and Governance Framework agreed that as long as sufficient explanation was given at the time of obtaining consent and participants then freely agreed to "*participate in the UK Biobank and all that that entails*", there would be no need to go back to the participants to obtain new consent for each and every proposed genetic study.[71] In addition to this imposing significant logistical and financial burdens upon the UK Biobank and being unduly troublesome to participants who may not want further contact, recontact would not be necessary as most genetic research undertaken using the Biobank would fall within the scope of the broad consent given by participants (even though this would not constitute full and informed consent). On this point, the *Nuffield Council on Bioethics*' views on the ethical acceptability of *genuine consent,* even if that consent is *not necessarily fully informed*, are highly instructive:

> *"The ethically significant requirement is not that consent be complete, but that it be genuine. Ensuring that consent is genuine is mainly a matter of care in detecting and eliminating lack of consent…Obtaining genuine consent requires medical practitioners to do their best to communicate as much as patients, volunteers or relatives can understand about procedures and risks, and to respect the limits of their understanding, and of their capacities to deal with difficult information. If all reasonable care is exercised, adequate and genuine consent may be established, although it will necessarily fall short of fully informed consent."*[72]

Nevertheless, in order for the consent to indeed be genuine in accordance with the Nuffield Council's definition, some commentators believe that procedural mechanisms should be established to deal with the small number of particularly sensitive kinds of research projects (for example, behavioural genetic research) or requests for access to Biobank data by particular kinds of researchers (for example, the tobacco industry) which may fall outside the scope of even broad consent.[73] The reaction in Iceland to the control of the Icelandic Health Sector Database being transferred to a private company illustrates that although many people may be willing to provide samples and allow access to their medical records for a public venture which aims at improving the health and welfare of the nation, these sentiments may not necessarily equate with a willingness to participate in research undertaken by commercial organisations aimed at generating profits.[74] Under the current proposed regulatory regime for the UK Biobank, if and when such ethically sensitive situations were to arise, the Ethics and Governance Council would decide whether or not access to the database should be granted, and if so, whether the particular research proposal

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[71] UK Biobank Ethics and Governance Framework: Summary of comments on Version 1.0, May 2004.

[72] 1995 Nuffield Council on Bioethics Report, Human Tissue: Ethical and Legal Issues "(Paragraphs 6.20-6.21)".

[73] "Tobacco firm to profit from cancer genes", The Guardian, November 12, 2001, describing Japan Tobacco's efforts to use genetic research to develop and sell vaccine and antibody-based products aimed at the prevention and/or treatment of lung cancer.

[74] *Supra* note 71, p.40

falls outside the scope of the broad consent granted and if participants need to be recontacted and new consent obtained.[75]

Although in fact a similar mechanism of obtaining broad consent with the safeguard of an Ethics Review Committee to identify research proposals which fall outside the scope of consent was also adopted in Japan, these issues of sensitive kinds of research or the ethics of certain kinds of private sector research have not drawn much discussion in Japan, and in contrast to the UK Biobank position, no mention of the fact that the resultant databases may be used by commercial entities needs to be made in the informed consent form.[76] As with the situation in the UK, it remains open to speculation quite how Japanese Ethics Review Committees will evaluate requests for access to genetic and medical data for use in potentially sensitive studies and to what extent the Japanese public would oppose the use of their genetic samples and medical information in certain kinds of (private sector) research.

2.6 Collection of Data From Medical Records

The UK Biobank will gather medical information and the medical records of participants and correlate this information with ongoing genetic analyses. This process is generally seen as a valuable aid in enabling researchers to "complete the health picture" and to increase the richness and accuracy of their analysis. The intention to link participants' samples to their medical records in the UK will be stated at the time of obtaining consent. One perhaps surprising aspect of genomic research in Japan is that at the current time there do not appear to be any plans to gather detailed information regarding donor's lifestyle patterns, medical records and environmental factors for correlative research, even in an anonymised form. Stuart suggests that this anomaly can be explained by the aforementioned fear of discrimination and the hypersensitivity to the stigma related to genetic congenital disease in Japan.[77] However, Masui and Takada have suggested that research on samples alone without correlation to medical records and environmental conditions is likely to be of limited scientific value, and have called for further discussion and clarification on the precise conditions and procedures for correlative research in order to ensure that a robust system for protecting privacy is in place.[78] It seems that clarification on this key issue will emerge from subsequent discussions between Ethics Review Committees and the Ministry of Health.[79]

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[75] Setting Standards, The UK Biobank Ethics and Governance Framework, 4 September 2003, p.3, stating that "..all proposals are subjected to peer review of their scientific quality, ethical review by an NHS Multi-centre Research Ethics Committee (MREC) and review by UK Biobank to ensure they are consistent with the participant's consent, UK Biobank's purpose and the Ethics and Governance Framework. This applies to all proposals, whether from universities, government, charities or commercial companies." *Also see* The UK Biobank, Ethics Consultation Workshop, 25 April 2002. p. 6, (discussing the issue of scope of consent). UK Biobank Ethics and Governance Framework, Background Document, Prepared by the Interim Advisory Group on Ethics and Governance, 10 October 2003, p.10.

[76] *See* Appendix I & II.

[77] Stuart, *supra* note 8, *at* 7.11.

[78] *Supra* note 5.

[79] Stuart, *supra* note 8 *at* 7.10.5.

2.7 Provision of Health Information to Participants

It is likely that some participants in genetic research studies may want to know the results of the analysis of their samples and the implications that this is likely to have for their health. Some participants may even expect this feedback as part of the *quid pro quo* for participation. Principle 13 of the *Fundamental Principles* establishes the general rule that each individual participant has the right to know about his/her own genetic information resulting from the research.[80] This should be explained to the participant when obtaining consent[81] If at the stage of initial enrolment it is discovered that the participant has a disease such as a monogenic disease, the explanation given to the participant or their representative should include information about the use of genetic counselling and he/she should be given access to genetic counselling as needed.[82] The "*bylaw regarding contracting out part of research without anonymisation*" in the *Ethical Guidelines* states that the chief researcher should either explain to the participants "regularly and as wanted", or make public the "progress, status and the results of analytical research" on their genetic information.[83]

However, at this point it is important to bear in mind that the term "*results*" in this part of the *Ethical Guidelines* seems to be referring to the information which arises as a primary "*result"* of the particular genetic research project being carried out by researchers, rather than to imposing a duty on researchers to provide "*results*" in the form of individual clinical diagnoses. Thus in many cases, even if a participant exercises his/her right to be informed of the results of the research, this will not always mean that the participant can obtain practically useful information, or that the participant will even be able to fully understand the meaning of the information disclosed.[84] On this issue, the *Fundamental Principles* state that:

> *"It is desirable that the researchers or medical practitioners fully explain to participants the meaning and usefulness of the genetic information obtained from the research, and the differences between research and diagnosis, and that they urge participants to understand and judge for themselves, before exercising their right to be informed, how genetic information arising as primary result of research differs from any diagnoses coming from the interpretation of that information."*[85]

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[80] *Fundamental Principles*, Principle 13, (*Right to be informed*).

[81] *Ethical* Guidelines, Chapter 3, (*Basic Attitude to Participants*) (9), (*Disclosure of genetic information*), *Bylaw regarding disclosure of genetic information*, (2).

[82] The current state of genetic counselling in Japan is discussed in critical terms in the explanatory notes to Principle 19 of *Fundamental Principles* (Social and Psychological Support), which state that the "systems of social and psychological support, and especially that of genetic counselling, currently remain in an unsatisfactory condition and require swift establishment and consolidation. The consolidation of the system itself underlies the understanding of the public on the human genome and the proper and effective implementation of research on the human genome. Therefore research institutions concerned should prepare supportive measures such as genetic counselling. It is desirable that those institutions that have not yet organised internal measures for support, should be prepared to use the facilities of other institutions."

[83] *Ethical Guidelines*, (5), (*Responsibilities of the chief researcher*), *Bylaw regarding contracting out of part of research without anonymisation.*

[84] *Fundamental Principles*, Principle 13 (*Right to be informed*), pp.24-25.

[85] *Id.*

The *Fundamental Principles* further elaborate upon the distinction between genetic research and clinical diagnosis, stating that:

> *"[a]s mentioned above, evaluation of the significance of each result of the research belongs in the domain of clinical diagnosis and is beyond the limit of the present Fundamental Principles…… Guidelines should be drawn up separately for genetic diagnoses."*[86]

Some exceptions to the rule that a Japanese participant has the right to know about his/her genetic information are elucidated in the *Fundamental Principles* and in the *Ethical Guidelines*. In the following cases, genetic information need not be disclosed to the participant:

1) In the case of large scale research projects, analytical research on the human genome/ genes is conducted to reveal a relationship between a certain disease and a gene or the function of a certain gene by comparing the genetic information of a large number of people or genes, and the genetic information of a single participant is not sufficient by itself to confer accuracy or reliability on a diagnosis of the condition of health or other medical aspects of the participant and thus disclosure to the participant would not be of sufficient significance. This decision should also be approved by the Ethics Committee.[87]
2) If the sample has been anonymised during the course of the research and can no longer be identified with the donor.[88]

In contrast, the general policy adopted by the UK Biobank is that of *not informing* participants of the results of ongoing research. This is due to the logistical difficulties involved and the higher legal 'duty of care' that would be imposed on providers of clinical diagnoses as opposed to researchers merely taking samples.[89] However, some observers in the UK have expressed discomfort with a possible scenario of researchers becoming aware of a participant having a serious medical condition for which a treatment is available, but then being prevented from disclosing this information to the participant and informing them of the risk because of the Biobank's information disclosure policy. As a compromise, it appears that exceptions to the general principle of not informing participants of the results of genetic analysis may be developed. This could perhaps entail UK Biobank participants being informed of any clinically relevant findings elicited during the initial consultations with the Biobank research nurse and then being asked to contact their GP about those findings.[90] However, it

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[86] *Id.*

[87] *Ethical Guidelines*, (9) (*Disclosure of Information*), *Bylaw regarding disclosure of information.*

[88] This second point is likely to be highly relevant in Japan, where as a general rule samples will be routinely anonymised before analysis is undertaken (*see* section 3.11, below). Stuart (*supra* note 8) reports that "none of the public databanks in Japan are understood to contain information from which DNA profiles could be generated. In the main, profile generation should only be possible where donors have made a request to be informed of the outcome of the results."

[89] UK BIOBANK Ethics and Governance Framework: Summary of Comments on Version 1.0, May 2004, p.20.

[90] The UK Biobank Ethics Consultation Workshop 25 April 2002, p.8

appears that the issue of feedback to participants is still undergoing consideration within the UK.[91]

2.8 The Right Not to be Informed

As a general principle, the participant has *the right not to be informed* of his/her genetic information resulting from genetic research, and the findings of the research may not be made known to the participant against his/her will. [92] Researchers are under an obligation to explain to subjects about their right not to be informed when obtaining consent. However, the *Ethical Guidelines* also contain a provision which permits researchers to override the participant's desire not to be informed in situations when it would be in the participant's best interests to be informed of the results of genetic analysis.[93] Factors to be taken into account by the Ethics Review Committee when making its deliberations include:

a) The availability of effective therapeutic measures;

b) The likelihood of the participant's blood relatives having the same disease or medical problem;

c) The effect on the lives of the participant's blood relatives and the health condition of the participant's blood relatives;

d) The stipulation of informed consent pertaining to disclosure of the research results.

2.9 Proxy Consent and Consent from those with Reduced Capacity

As a general rule under the Japanese regulatory framework, samples should not be taken from an individual who lacks the capacity to consent (e.g. if they suffer from a condition such as dementia or if they are a minor), nor should samples be used from the deceased. However, this is qualified by an exemption which allows researchers, in cases where the study is of *significant social benefit* and could not be undertaken without a sample from the specific individual lacking capacity to consent, to take proxy consent from a representative.[94] Whether or not an individual has the capacity to consent should be judged in as scientifically and objectively a manner as is possible. Thus, a medical practitioner who is unconnected with the research in question should make the actual decisions from an objective standpoint. Principle 6 of the *Fundamental Principles* stipulates that "an individual incapable of giving his/her own consent should not be involved whenever the research could be conducted equally well without the participation of that individual".[95] Once an Ethics Committee has given approval to proxy consent, researchers may contact the potential

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[91] UK Biobank Ethics and Governance Framework, Background Document, Prepared by the Interim Advisory Group on Ethics and Governance, 10 October, 2003, p.8.

[92] *Fundamental Principles*, Principle 14.

[93] *Ethical Guidelines*, Chapter 3, (*Basic Attitude to Participants*), (9) (*Disclosure of genetic information*), *Bylaw regarding the non-disclosure of genetic information.*

[94] *Fundamental Principles*, Principle 6, (Individuals who do not have the Capacity to Consent). However, the precise definition of *significant social benefit* is not elaborated in either of the guidelines.

[95] *Id.*

participant's representative, and obtain full and informed consent in accordance with the general consent rules described above.[96]

The '*Bylaw regarding the basic idea about the selection of the participant's representative*' in the *Ethical Guidelines* provides that the chief researcher should select the participants' representative from the following persons in the following order, with due consideration given by researchers to the participant's particular familial structure:

a) The participant's spouse; adult offspring; a parent; an adult sibling or grandchild; a grandparent; a relative living together; a person considered equivalently close to the participant.

b) A voluntary guardian; a person with parental authority; a lawful guardian or an assistant.[97]

The procedures to select the representative should be clearly described in research plans and undergo the review of the Ethics Committee. When giving consent on behalf of the participant, the representative should take sufficient precautions that the rights and interests of the participant are protected and would not be infringed. In a case when the participant is a minor above a certain age, it is desirable that consent also be obtained from the participant him/herself. There are no provisions in the two sets of guidelines for advance directives by future participants before they become incapacitated.

2.10 The Withdrawal of Consent

In Japan, under the *Fundamental Principles* and the *Ethical Guidelines*, the rights of a research subject to withdraw their consent for the use of their samples and resultant data in a project hinges upon the issue of whether a particular sample can be linked to the individual who donated it.[98] In principle, consent can be withdrawn at any point without disadvantage to the participant if the sample can still be attributed to its donor. In these cases, the sample itself and the data derived exclusively from it should be destroyed.[99] However, consent cannot be withdrawn once the sample has become unidentifiable, it is no longer linked to its donor, or it is stored in such a way that the linking is impossible.[100]

This information about the right to withdraw consent, and its limitations, should be given in advance of obtaining the donor's informed consent.[101] When the period of

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[96] *See* the general consent rules outlined in Section 2.3 of this report.

[97] *Ethical Guidelines*, Chapter 3, (8)(*Informed Consent*), (*Basic Attitude to Participants*), *Bylaw regarding the basic idea about the selection of the participant's representative.*

[98] *Fundamental Principles*, Principle 10, Withdrawal of informed consent:

1. The consent for a donated sample to be used for research may be withdrawn providing that the said sample can be linked to its participant.

2. A participant should not be disadvantaged even if s/he withdraws his/her informed consent.

[99] *Fundamental Principles, Principle 10, Withdrawal of informed consent* states that "[w]hen the consent to use a sample is withdrawn, the sample itself and the results derived exclusively from it should be destroyed."

[100] *Id.*

[101] *Id.*

preservation of samples etc. as prescribed in the research protocol has elapsed, the chief researcher should destroy them in accordance with the conditions agreed on with the participants or their representatives. This provision, however, does not apply to cases where samples etc. are preserved by the chief researcher himself or provided to a human cell, gene or tissue bank. Consent cannot be withdrawn for samples that are stored in banks or are commercially available.[102] The research results need not be destroyed in instances where they have already been made public.[103]

The two sets of Japanese guidelines do not make any provision for individual participants to selectively opt out of individual projects involving a particular kind of research, nor are there any alternatives to complete withdrawal of consent to participate, such as the model of *discontinued participation* proposed in the UK Biobank *Ethics and Governance Framework*.[104]

2.11 Withdrawal of Consent by the Relatives of a Deceased Research Subject

The issue of whether the relatives of a deceased participant in a Biobank can exercise control over their deceased relative's samples and medical records by withdrawing the original consent for participation was considered in a 2004 ruling by the Supreme Court of Iceland.[105] The court held that the daughter of a deceased research subject who participated in a biobank had legal standing to prevent the right to prevent the transferral of their relatives' medical data into a genetic database. The Court's reasoning was founded upon the argument that as the plaintiff and her deceased father both shared genetic characteristics, the information in the database would allow inferences to be made about the plaintiff herself, and therefore her father's medical records fell within the scope of personal information protected by the plaintiff's constitutional-protected right to privacy.[106]

Although the Japanese guidelines predate the Icelandic Supreme Court ruling, they follow a similar pattern of reasoning. The Japanese approach is to stress that researchers should respect the feelings and wishes of the participants surviving family and give due consideration to the fact that genetic information of a dead person is shared by his/her blood relatives.[107] Consequently, the appointed representatives of the participant may also withdraw their consent for the use of the participant's sample in accordance with the above-mentioned principles. The dead participant's representative should be a person who is considered to be able to represent the will that the dead participant was supposed to have while alive. The participant or his/her

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[102] *Ethical Guidelines*, Chapter 4 (*Handling of Samples etc.*), (12) (*Methods of preservation and destruction of samples etc*).

[103] *Ethical Guidelines* Chapter 3, (*Basic Attitude to Participants*), (8) (*Informed Consent*), *Bylaw regarding exceptions concerning destruction of samples, etc. and research results.*

[104] UK Biobank Ethics and Governance Framework, Background Document, Prepared by the Interim Advisory Group on Ethics and Governance, 10 October 2003, I.B.6 Right to withdraw.

[105] Icelandic Supreme Court, No.151/2003.

[106] For a critique of this rationale, *see* Gertz, R. "An analysis of the Icelandic Supreme Court judgement on the Health Sector Database Act", (2004) 1:2 *SCRIPT-ed*, arguing that the reasoning employed by the Supreme Court may lead to other complicated questions, such as whether an individual would also have legal standing to object to their *living* parent's data being included in the database.

[107] *Ethical Guidelines*, Chapter 3, (*Basic Attitude to Participants*), (8) (*Informed Consent*), *Bylaw regarding the basic idea about the selection of the participant's representative in case where the participant is a dead person.*

representative can withdraw their consent at any time without penalty by expressing the intention of doing so in writing. When consent has been withdrawn, the chief researcher should *in principle* anonymise and destroy the samples, etc. provided by the participant and the research results concerning the participant.[108] However, it is not entirely clear if the relative of a deceased research subject will first have to be appointed by the chief researcher of a research institution as a representative before he/she can exercise this right. How this mechanism will operate if the institution refuses to appoint the surviving relative of the deceased as the representative, or how institutions should prioritise competing interests if a conflict should emerge amongst relatives is a point for further discussion.

As with the withdrawal of consent by the participant themselves, a number of limitations apply to a representative's right to withdraw from a research project. Consent can not be withdrawn if research samples have been anonymised so that they cannot be linked to the participant, or if there is very little possibility that personal information could be elicited from them if they were not destroyed and it would be prohibitively expensive to destroy the samples, or if the research results have already been made public.[109]

3. Privacy

3.1 The Protection of Personal Medical Data in Japan

As the analysis of genetic information can reveal an individual's current physical condition and their predisposition for developing genetic disease, there is the fear that these highly sensitive data could be used to discriminate against individuals in the context of employment or insurance. This anxiety is highly accentuated in Japan, where inheritable disease has traditionally been stigmatised and where even public discussion of the issues raised by inheritable genetic disorders is generally shunned.[110] The Japanese Medical Association has issued repeated warnings that this particular attitude towards genetic disease in Japan, combined with the current distrust with which Japanese medical and research professionals are regarded, is likely to result in a general reluctance to participate in genetic research programmes- particularly if a credible and secure system of personal data protection cannot be demonstrated to the Japanese public.[111] A number of observers have therefore predicted that the issue of privacy, above all others, is likely to be the one which will most significantly shape public perceptions of genetic research and analysis in Japan.[112]

This section describes and analyses the framework for protecting privacy put into place by the *Fundamental Principals* and the *Ethical Guidelines*. However, before moving on to an examination of the privacy rules established by the two sets of Guidelines, a brief mention will be made of the 2003 *Personal Information Protection*

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[108] *Id.*

[109] *Ethical Guidelines*, Chapter 3, (*Basic Attitude to Participants*), (8) (*Informed Consent*), *Bylaw regarding exceptions concerning destruction of samples and research results.*

[110] *See* Stuart, *supra* note 8.

[111] *Supra* note 1

[112] "Dispute over data privacy halts cancer study" Nature, (2003), Vol 424.

Law (Japan), and the duty on medical professionals to protect the confidentiality of patient's personal information set out in Japanese criminal law.

3.2 The Japanese Data Protection Law 2003

The Japanese *Data Protection Law*, which passed the Japanese parliament in May 2003, is the first statute to comprehensively regulate the use of information in the private sector in Japan.[113] The law places controls on the way in which personal information is collected and retained, and prevents the disclosure of personal information to third parties without the consent of the individual concerned. However, the law itself was designed more specifically to deal with regulating the use of private information in the fields of commerce and business than to protect personal medical information, and the exemption carved out by Paragraph 50, Section 1, Subsection 3 of the *Data Protection Law* excludes academic research from the need to conform to the provisions of the *Law*. Although the paragraph 50 exemption does not specifically mention medical information or genetic research, it is generally believed that the *Data Protection Law* does not apply to genetic research.[114] However, at the current time it is not clear if genetic research conducted by public/private consortia will also fall within the scope of the paragraph 50 exemption of the *Data Protection Law*.

3.3 The Legal Duty to Protect the Confidentiality of Patient's Information

The medical profession in Japan has long been subject to laws and regulations which have placed its workers under a professional duty to protect confidentiality. Physicians, pharmacists and midwives have all been regulated by the *breach of confidence* provisions of section 134 of the *Criminal Code* (Law No.45, enforced in 1907), Article 100 of the *National Civil Service Law* (Law No. 120, enforced in 1947), and other relevant laws. Even those working in the medical field lacking professional qualifications have also been subject to separate laws which establish a legal duty to protect patient confidentiality. However, the duty to protect the confidentiality of patient's/ research subjects' medical information is not absolute, and a number of exceptions exist whereby physicians may use the data for purposes other than those agreed and decided, or pass the information on to third parties in cases where this is necessary to preserve human life, health or property; or to maintain public health and sanitation or to protect the welfare of children.[115]

Having established that the Personal Information Protection Law will have little impact on genomic research, but that Japanese physicians were nevertheless already under a legal duty to protect the confidentiality of their patient's records, we now turn to examine the regime established by the *Fundamental Principles* and the *Ethical Guidelines*.

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[113] Kojin Jyoho no Hogo ni Kan Suru Ho (2003) (The Data Protection Law, 2003) http://www.kantei.go.jp/jp/it/privacy/houseika/hourituan/030307houan.html (*Japanese only*) (*last visited September 1st 2004*). The law will be fully in force after a two-year grace period in May 2005.

[114] Kobayasi, Y, *Kojin jyoho hogo ho to kanja no kenri*, (The Personal Information Protection Law and Patient Rights), [*Japanese only*] Jurist (No.1253), (2003).

[115] Ishikawa, K., *Iryou bunya ni okeru kojin jyoho hogo* (The protection of personal information in the medical sphere), Jurist (2003), No.1253, (*Japanese only*).

3.4 The Commitment to Confidentiality

One of the key themes permeating both sets of guidelines is *anonymity*. The *Ethical Guidelines* and the *Fundamental Principles* both stress that at all points during the collection, storage, transfer and utilisation of human biological materials, the anonymity and privacy of the research subject must be protected. *Principle 11* of the *Fundamental Principles* outlines in broad terms the importance of protecting the confidentiality of personal genetic information.[116] The explanatory notes to the *Fundamental Principles* also impose an obligation on research institutions to establish a control system for the safekeeping and protection of the personal information related to providing samples, including the separate storage of information which can link the sample and the donor.[117]

The strict confidentiality of personal information is also enshrined as one of the basic principles of the *Ethical Guidelines*, and the duties of researchers and heads of research institutions in protecting subject privacy are delineated in considerable detail.[118] The basic responsibilities of researchers are described in *Chapter 2* of the *Ethical Guidelines*, and are stated as being the protection of personal information, efficiently responding to complaints about standards of data governance, and the prevention of the disclosure of personal information (unless this disclosure is justified).[119] The sanctions for breaching the provisions of the guidelines with regards to maintaining the confidentiality of personal information include the penalties described above under the *breach of confidence* provisions of section 134 of the *Criminal Code* (Law No.45, enforced in 1907), demotion of the researchers involved and the withdrawal of research funding. Principle 12 of the *Fundamental Principles* also provides that if a breach of confidentiality occurs, the participant who has sustained damages from that disclosure is entitled to receive compensation or indemnity.[120] However, these legal remedies are not elucidated in any great detail within the *Fundamental Principles* themselves.

3.5 The Role and Responsibilities of the Personal Information Manager

Both the *Fundamental Principles* and the *Ethical Guidelines* stipulate that research institutes have an obligation to appoint a personal information manager, who will manage personal information processing activities and construct a clearly defined chain of command for the control of personal information for each research project.[121] The personal information manager should be an *individual who is legally prohibited* from disclosing secrets that he/she has come to know in the performance of their duty.[122] The personal information manager will also oversee the process of the

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[116] *Fundamental Principles* Principle 11 "*The Protection and control of genetic information and establishment of a control system*".

[117] *Id.*

[118] *Ethical Guidelines*, Chapter 2, (*Responsibilities of Researchers*), *Bylaw regarding confidentiality of personal information.*

[119] *Ethical Guidelines*, Chapter 2, (*Responsibilities of Researchers*), (3) *Basic responsibilities of all researchers, etc.* (5).

[120] *Fundamental Principles*, Principle 12 (3).

[121] *Ethical Guidelines*, Chapter 2. (*Responsibilities of Researchers etc.*), (4) *Responsibilities of the head of a research institution, Bylaw regarding confidentiality of personal information.*

[122] *See* section 3.2, *above.*

anonymisation of research samples, is responsible for keeping any identifying information stored separately from the sample itself and holds the "keys" to unlock anonymised data/samples when requested by researchers and authorised by the Ethics Review Committee.[123]

3.6 The Anonymisation of Research Samples

As a general rule, all samples should be anonymised before analytical research on the human genome/genes is conducted in order to protect and maintain the privacy of the participants.[124] The *Ethical Guidelines* define two types of anonymity:

a) *Relative anonymity*, where samples may still be linked to subjects. Samples etc. are made unidentifiable, but a table that links them with codes or numbers assigned to research subjects is retained to allow identification if necessary.

b) *Absolute anonymity* where samples cannot be linked to subjects. Samples etc. are made irreversibly non-identifiable without retaining a table that links them to codes or numbers assigned to research subjects.

A two stage process has been constructed for the anonymisation of donor information. The first stage of anonymisation occurs when subjects donate materials to medical institution, and a second level of anonymisation occurs if this information is transferred for incorporation into a larger, central database. In the first stage, samples taken and used in research by the medical institution retains information which can be used to identify the subject, but the procedures for linkage and the information necessary are tightly controlled by the personal information managers. Stuart describes the procedures for anonymisation and holding samples separately from identifiable medical and personal information from in the following way:

> *"Managers appointed to supervise the protection of donor information provide each sample with a unique bar code, containing donor information. Details of the coding are kept on a stand-alone workstation, protected by fingerprint operated mouse controls and a hard disc drive password entry system. Paperwork relating to the donors is kept in a high security safe. The bar-coded sample is then passed (along with the age of the donor) to the research team."*[125]

The second stage of anonymisation occurs when research data is transferred into a central database. The data, along with the age of the donor, are fed into an online computer connected to the central database. Linkable now only by age and under normal circumstances amongst an array of data for similar aged donors, the data and donor should no longer be unequivocally linkable. Aggregation further reduces the chances of the sample being linked to a particular individual.[126]

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[123] *Fundamental Principles, Principle 11, (2).* The explanatory notes to this section stipulate that research institutions must appoint "custodians of the personal information, who will protect identifying information and personal information, and manage the separation and connection of the different categories of information". *Also see Ethical Guidelines*, (6) *Responsibilities of the personal information manager* (1).

[124] *Ethical Guidelines*, Chapter 2. (*Responsibilities of Researchers etc.*), (5) *Responsibilities of the chief researcher, Bylaw regarding research without anonymisation* (6).

[125] *See* Stuart, *supra* note 8.

[126] *Id.* Stuart states that all MHLW national research institutes are required to follow this procedure.

However, some observers have suggested that perfect anonymisation is extremely difficult, and the chance of linking samples to an individual will always exist. Whereas this generally constitutes the starting points on discussion regarding anonymisation within the UK, the great difference with discussion and debate in Japan is that discussion flows from the presupposition that perfect anonymisation is possible. This, according to Masui and Takada, influences the quality of the discussion in the two countries.[127]

As mentioned above, one perhaps surprising aspect of genomic research in Japan is that at the current time there do not appear to be any plans to gather detailed information regarding donor's lifestyle patterns, medical records and environmental factors for correlative research, even in an anonymised form. Stuart suggests that this anomaly can be explained by the aforementioned fear of discrimination and the hypersensitivity to the stigma related to genetic congenital disease in Japan.[128] Masui and Takada have suggested that research on samples alone without correlation to other personal and medical information is likely to be of limited scientific value, and have called for further discussion and clarification on the precise conditions and procedures for correlative research, especially in longitudinal cohort studies, and to ensure that a robust system for protecting the privacy of participants is in place.[129]

It is unclear under the current guidelines how anonymisation will operate if the same institution is carrying on multiple projects, as potential modalities for transferring data between projects have not yet been fully elaborated. Stuart observes that in circumstances where hospitals are likely to have insufficient patients for a satisfactory association study and study methods between researchers vary considerably, useful comparisons of data will be difficult to make.[130]

3.7 Exceptions to the Principle of Protection of Subject Anonymity

Although the importance of the anonymisation of research samples is given considerable emphasis and is one of the principal mechanisms through which confidentiality is maintained, it is nevertheless accepted by the Ministry of Health Labour and Welfare that there is value in certain circumstances (e.g. when disease related and where an effective method of treatment exists) in being able to link research data to the sample donor. In such circumstances, under conditions yet to be fully determined and with the authorisation of the Ethics Review Committee, heads of research institutes will have the authority to link research data to the sample donor.[131] Where the disease is a hereditary one and beneficial medical intervention is not

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[127] Masui & Takada *supra* note 5.

[128] Stuart, *supra* note 8, reports that "it is broadly accepted that it is difficult to construct patient linkable databases in Japan, principally due to the fear of discrimination and sensitivity to information linking the patient to genetic disease. Linkable information is also recognised to be of limited value where additional essential information such as environmental conditions is not routinely collected."

[129] *Supra* note 5.

[130] *See* Stuart, *supra* note 8.

[131] *Id.*

possible, a decision on whether or not it would be appropriate to permit linkage is also currently under review by the MHLW.[132]

A second exception to the principle of anonymity outlined above is that samples may be provided to an 'outside institution' or transferred to sub-contractors *without anonymisation* if the participant or his/her representative has consented to provision of samples, etc. or genetic information to an outside institution without anonymisation and the research protocol, which has been approved by the Ethics Review Committee and authorised by the head of the research institution, stipulates the provisions of samples, etc. or genetic information without anonymisation.[133] Here, the issue of privacy is to an extent recast as an issue of autonomy.

The "*safe harbour*" provisions of the *Ethical Guidelines* specify that if a Japanese research institution engages in joint research with overseas researchers, the Japanese personal information managers and Ethics Review Committees must ensure that the foreign receiving institution has standards of data governance that are either equivalent to or higher than those provided in the *Ethical Guidelines* before authorising the transfer of identifiable data and other sensitive information.[134]

3.8 Disclosure of Genetic Information to Persons Other than the Participant

In many cases, informing a specific individual of the results of a test for a genetic disorder will have serious implications not only for the individual concerned, but also for his/her blood relatives, who may also share the same genetic condition. The *Fundamental Principles* state that at the time of obtaining informed consent, researchers should explain to participants about the implications of the result of a genetic test for family members, and allow the participant to make a judgement beforehand with regards to whether they would wish to inform blood relatives of the results of the participant's genetic analysis or whether they would prefer that this information remains confidential. In the eventuality that a conflict emerges between the right of the participant to keep the information private and the right of the blood relative to know about their own health, the Japanese regulatory framework maintains the flexibility to give priority to the latter.[135] Even in cases where participants have stated that they do not wish other parties or blood relatives to be informed of the results deriving from analysis of their genetic information, if a participant's genetic information has been found to indicate that there is a genetic effect which is very likely to endanger the lives of the participant's blood relatives, and there is an effective therapeutic measure to deal with the genetic effect, the *Ethical Guidelines* authorise Ethics Review Committees to permit the disclosure of genetic information to the participant's blood relatives even against the participant's wishes.[136] The chief researcher should consult with the Ethics Review Committee on the decision of whether or not to reveal the information to blood relatives, the extent of the

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[132] *Id.*

[133] *Ethical Guidelines*, Chapter 2. (*Responsibilities of Researchers etc.*), (5) (*Responsibilities of the chief researcher*), *Bylaw regarding provision of samples, etc. or genetic information to an outside institution without anonymistion.*

[134] *Ethical Guidelines*, Chapter 1. (*Basic Ideas*), (2) (*Scope of application*), *Bylaw regarding international joint research.*

[135] *Fundamental Principles, Principle 15.*

[136] *Ethical Guidelines*, Chapter 3. (*Basic Attitude to Participants*), (9) (*Disclosure of genetic information*), Bylaw regarding disclosure of genetic information to persons other than the participant.

information to be disclosed and the method of disclosure, before informing blood relatives. These provisions therefore seems to grant researchers the *discretion to inform* participants of the results of genetic analysis, rather than imposing an *obligation to inform* in all cases.

As in the UK, scant consideration has been paid in Japan to possible modalities for protecting the rights of *blood relatives of a research subject who do not wish to know* their own genetic information, but where informing the research subject of their genetic test result will nevertheless often amount to indirectly informing blood relatives of their own genetic predisposition to certain diseases.[137]

4. Relationship with Society

4.1 Governance Structure and Accountability

All research institutions in Japan at which analytical research on the human genome/genes is conducted are required to install an Ethics Review Committee.[138] It is envisaged that the Ethics Review Committee will oversee all stages of genome research and act as the overarching ethical control mechanism, ensuring compliance with the guidelines, transparency and accountability. Ethics Review Committees will screen all research proposals submitted by researchers and have the power to make recommendations to alter research protocols, or even to reject them outright. Approved research protocols must be adhered to, and regular monitoring will ensure against unethical research practices. The *Ethical Guidelines* define the role and the nature of the interactions between researchers, heads of research institutes and Ethics Review Committees. The *Ethical Guidelines* also provide details regarding the composition of Ethics Review Committees, stipulating that Committees should ideally be composed of members trained in social sciences and cultural issues, and crucially, it is stated that it is *desirable* that more than half of the members of the Ethics Review Committee should be independent of the research institution which it is overseeing. [139] However, this requirement is relaxed with the provision that if the research institute encounter difficulties in engaging independent committee members, the number can be reduced to one single external ethics reviewer.[140]

On-the-spot investigations will be conducted at research institutions by outside experts to ensure compliance with the guidelines and to confirm that the individual research protocols are being adhered to.[141] The head of a research institution must send copies of the regular reports on the operational status of research and the reports

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[137] *See generally,* Laurie, G., *Genetic Privacy: A Challenge to Medico-Legal Norms,* (2002), Cambridge University Press.

[138] *Ethical Guidelines*, Chapter 2, (*Responsibility of Researchers, etc.*) (4) (*Responsibilities of the head of a research institution*), (4) Bylaw regarding the requisites for the personal information manager: "The head of a research institution should install an Ethics Review Committee as an advisory body for examination of the validity of execution, etc. of analytical research on the human genome/genes."

[139] *Ethical Guidelines*, Chapter 2, (*Responsibilities of Researchers, etc.*), (7) (*Responsibilities of the Ethics Review Committee and its organisation*), *Bylaw regarding the organisation of the Ethics Review Committee.*

[140] *Id.*

[141] *Ethical Guidelines*, Chapter 2, (*Responsibilities of Researchers, etc.,*) (4) (*Responsibilities of the head of a research institution*) *Bylaw regarding on-the-spot inspection by an outside expert(s).*

of on-the-spot inspection by outside experts to the Ethics Review Committee. The Ethics Review Committee is in turn obliged to send an annual report on the operational status of research projects to the Japanese Ministry of Health, Labour and Welfare.[142] The Ministry of Health will review current policy and issue further guidance on the basis of the collected reports, and may place information in the public domain in order to promote transparency and to promote the public's freedom of access to information.[143] The adequacy of these arrangements is still being debated in Japan.

4.2 Intellectual Property Rights

Genetic databases are primarily designed as resources for the statistical analysis of the role of specific genes in the onset of genetic disease, and are not expected in themselves to lead to patentable inventions that will return significant income either to researchers or to the biobanks in the short-term.[144] However, it is anticipated that in the medium-to-long-term, research conducted using the data or samples from genetic databases may support the development of inventions that generate revenue.[145] There is also the possibility that biobank researchers may generate cell lines from scientifically useful biological samples, which could then be marketed as research tools.[146] Japanese researchers are fully aware of the importance of securing intellectual property protection on the results of their research. Japanese patent law permits the patenting of biotechnological products and processes on similar terms to the patent laws of the United States and the European Union.[147]

Stuart observes that where the Millenium projects give rise to patentable information, such as the identification of the role of certain genes in the pathology of genetic disease, the Japanese MHLW, via its *Organisation for Pharmaceutical Safety and Research* (OPSR), will file patent applications. Revenue generated by the intellectual property will be divided between OPSR and all those having had an input, including, where appropriate, universities, individual research institutes and companies.[148] This arrangement is likely to be a powerful incentive to the public sector research community.[149] Given this strong emphasis on the commercialisation and patenting of research results as an aspect of Japanese industrial policy, it has been important for the two sets of guidelines to attempt to construct a uniform system for the allocation of property and intellectual property rights in samples and the valuable genetic information contained therein at different stages of research and development.

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[142] *Ethical Guidelines*, *Ethical Guidelines, Enforcement, etc. of the Ethical Guidelines for Analytical Research on the Human Genome/ Genes, Reporting of Installation and Operation of Ethics Review Committee.*

[143] *Id.*

[144] UK Biobank Ethics and Governance Framework, Version 1.0, 24 September 2003, (*for comment*), p 27.

[145] *Id.*

[146] *See* the UK Biobank Ethics Consultation Workshop 25 April 2002, pp.9-10.

[147] For a detailed comparison of the patentability criteria for biotechnology in the United States, the European Union and Japan, *see* the Trilateral Studies website: http://www.european-patent-office.org/tws/sr-3.htm (*last visited September 1st 2004*).

[148] *Supra* note 8.

[149] *Id.*

In alignment with the trend in most developed countries, the *Fundamental Principles* elects to resolve any potential uncertainty in this area through the use of the informed consent as a mechanism to mediate the relationship between the researcher and the participants in relation to property/intellectual property rights and to define the legal status of biological materials and the genetic information contained therein. Principle 17 of the *Fundamental Principles* states that:

> *"Researchers or research institutions can claim intellectual property rights such as patent rights based on the results of their research. A participant who simply provides a research sample cannot claim intellectual property rights relating to the sample, since the value of those intellectual property rights is brought about by scientific actions of the researchers, or by the ingenuity of those persons who make use of the outcomes of that research, and is not attributable to the provided sample or to the genetic information contained in it. It is desirable that it be made clear to participants, at the time that their informed consent is obtained, that they cannot automatically claim the intellectual property rights."*

Principle 17 of the *Fundamental Principles* (*Gratuitousness and related principles*) then goes on to state that when researchers are obtaining written informed consent, there explanation must contain a statement to the effect that i) research samples should be provided gratuitously; and ii) in the event that an outcome obtained as a consequence of a research project becomes the subject of intellectual property rights or other rights, these rights are not attributed to the participant.[150]

It is unclear how a case with similar facts to *Moore v. The Regents of the University of California*, where researchers filed patents on commercially valuable excised biological material without the subject's knowledge or consent, would be decided under the provisions of Japanese law.[151] To date, there have not been any cases in Japan which have explicitly considered the issue of whether an individual has property/ intellectual property rights over biological materials extracted from their body, nor is the potential conflict of rights which may arise in such a case clarified by being specifically addressed in any Japanese legislation. Similarly, the Japan Patent law does not contain any provision equivalent to Recital 26 of the Biotechnology Directive, which states that a participant from whose body the biological material is taken must have had an opportunity of expressing free and informed consent in accordance with national law.[152]

In an attempt to address this complex and nebulous question, Sumikura points out that according to Article 246 of the *Japanese Civil Code*, when a person has added their workmanship to the property of another person, the ownership of that work

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[150] *Fundamental Principles,* Principle 17. *Also see Appendix I*, (15).

[151] *John Moore, Plaintiff and Appellant, v. The Regents of the University of California et al., Defendants and Respondents*, 793 P.2d 479 (Cal. 1990).

[152] Recital 26 of the Directive 98/44/EC of the European Parliament and of the Council of Europe of 6 July 1998 on *the* legal protection of biotechnological inventions states that "[w]hereas if an invention is based on biological material of human origin or if it uses such material, where a patent application is filed, the person from whose body the material is taken must have had an opportunity of expressing free and informed consent thereto, in accordance with national law".

nevertheless still belongs to the original owner of the materials.[153] However, Article 246 also states that when the economic value resulting from that workmanship far exceeds the value of the original materials themselves, the person adding the workmanship acquires ownership of that work. Since research materials such as cell lines used as research tools would generally have far greater economic value as a result of manipulation by a researcher than would the extracted materials themselves in their 'raw' state, Sumikura suggests that it may be reasonable to tentatively conclude that their ownership would therefore lie with the researcher rather than with the source of the biological materials in question. However, Sumikura also suggests that if a case with similar facts to *Moore* were to be decided in Japan, a judge may take the view that a research subject in a certain sense, 'owns' the biological materials extracted from their body (in terms of traditional property rights rather than registered patent rights) until they are conveyed or title is transferred through conferring consent.[154] As stated above, it seems likely that if the issues of intellectual property rights are explained and dealt with in the consent form, there will be no need for a Japanese court to consider these questions.

4.3 Dissemination of Information

With regards to the dissemination of information and research results in general, the two sets of guidelines state that in principle, the results of research should be publicly disclosed, in line with the stated objective of improving the health and welfare of humanity and of each human being.[155] The proviso which applies here is that the confidentiality of research results may be maintained for the time period in which it is reasonable to do so in order not to compromise intellectual property rights or for other purposes relating to ongoing research. The UK Biobank *Ethics and Governance Framework* has a similar statement, but also contains a particular emphasis on the publication of negative findings and the development of a system for the "archiving of such materials."[156]

4.4 Benefit Sharing

One of the points related to the legal ownership of biological samples is the issue of whether payment should be paid to the sample donor. Sumikura states that although it could be argued that a monetary expression of appreciation could be paid to donors of blood samples in order to promote research of gene analysis, this is equivalent to assigning a monetary value to samples originating from the human body, and is generally viewed in Japan as being ethically improper and in violation of the principle of altruism which has traditionally governed the collection of biological samples.[157]

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[153] Sumikura, Koichi, *Bioethical Issues of IPR- Theme 2 Consent to Patents and Profit, Genome Business and Gene Patents*, (submitted for the Roundtable discussion on Bioethical Issues of IPRs, University of Cambridge, 28 and 29 March, 2003).

[154] *Id.*

[155] *Fundamental Principles*, Principle 25, *Public Disclosure of outcomes of the research and return of benefits to society*.

[156] *See* UK Biobank Ethics and Governance Framework, Background Document, Prepared by the Interim Advisory Group on Ethics and Governance, 10 October 2003, p.13 *Also see* Ethics and Governance Framework, Version 1.0 24 September 2003 (*for comment*) p. 27.

[157] *See* Sumikura, *supra* note 153.

This is essentially the same position adopted by the UK Biobank *Interim Advisory Group on Ethics and Governance* which stated in a 2003 report that it saw "no issue" in regards to whether participants should receive remuneration for participation in the Biobank- "the expectation simply needed to be stated: Volunteers should not expect to be paid for their participation in UK Biobank."[158]

Neither the *Fundamental Principles* nor the *Ethical Guidelines* mention specific provisions for benefit sharing of the profits of genetic research with research participants, other than that the beneficial results of the scientific research itself will benefit to society. However, Kyushu University has taken the lead on this issue in a pioneering example of benefit sharing with the inhabitants of the town of Hisayama in Fukuoka, where the University been conducting health-related studies for over thirty years. A recent study has been commenced to investigate the genetic factors involved in lifestyle-related illnesses using the genetic information and medical data of local residents, and the University decided to reinvest income generated from any patents filed to provide educational activities and to improve the health and welfare of the local residents.[159] Sumikura considers the Hisayama project and its benefit sharing structure to be an ethically laudable means of compensating sample donors following the patenting of research results.[160] Kyushu University's commitment to benefit sharing is also consistent with the principles of solidarity and reciprocity expressed in the *Fundamental Principles* and the *Ethical Guidelines*, and may help to overcome some of the current negative publicity surrounding medical research in Japan.

5 Adequacy of the Current Guidelines and Possible Future Developments

Despite the *Fundamental Principles* and the *Ethical Guidelines* being described by the Japan Pharmaceutical Association as "the strictest in the world" with regards to the regulation of genetic research, the two sets of guidelines have attracted some criticisms within Japan, most notably from the highly influential Japanese Medical Association (JMA).[161] The JMA has publicly stated that the current regulations are "[u]nclear on who owns genetic data, and leave too much discretion to advisory committees."[162]

Since the publication of the two sets of Japanese guidelines, the methodology used to collect medical information in one particular epidemiological study has drawn a particularly hostile response from the JMA.[163] Criticisms stemmed from the fact that the work of collecting personal lifestyle data for a cancer study of 6,000 residents of Kumano-cho, a small town near Hiroshima, was contracted out to ordinary citizens

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158 UK Biobank Ethics and Governance Framework, Background Document, Prepared by the Interim Advisory Group on Ethics and Governance, 10 October 2003, p.11, I.B.8

159 Yomiuri Shimbun, November 9, 2002, Morning edition, page 2.

160 This position also finds support in Article 19, "Sharing of Benefits", of the UNESCO International Declaration on Human Genetic Data (i-vii) (adopted by the 32nd session of the General Conference of UNESCO on 16 October 2003).

161 *Supra* note 4.

162 *Id.*

163 *Supra* note 4.

who were under no legal obligation to protect the confidentiality of the information they were handling. The relevant provisions of the *Ethical Guidelines* state that personal information managers and assistant personal information managers must be individuals who have a legal duty to maintain the confidentiality of medical information, and must establish a clearly defined chain of command with privacy ensured at each stage.[164] However, no mention is made of the requisite status of staff employed to assistant in the collection of information in genetic studies, and whether or not they must also be individuals who are under a legal duty to maintain the confidentiality of medical information. It has been suggested that the two sets of Guidelines contain several such areas of potential uncertainty, and that occasional revisions to the guidelines to clarify specific issues are expected.[165] The JMA's comments are indicative of the current distrust between physicians and clinical researchers in Japan.[166] In his analysis of the JMA's motivations, Masui has stated that he believes that the JMA is attempting to use this particular incident to exert political pressure on the relevant Ministries and clinical researchers in order to "win a greater say for physicians in planning and reviewing such projects."[167] This dispute is likely to continue, but in the meantime, the fact that this incident was widely reported in the Japanese media will likely have a negative impact upon public perceptions of the current standards of privacy protection in genetic research.

The adequacy of the methods for the enforcement of the guidelines has also been called into question in Japan. Although the Ministry of Health does back the current guidelines with the threat of sanctions (such as the withdrawal of research funds from institutions which violate the *Ethical Guidelines*) it is unclear what normative impact the guidelines will have on private research institutes which are not dependent on state funding.[168] Some commentators have stated that in addition to the guidelines, formal legislation backed with legal sanctions is urgently needed to regulate the collection, storage and use of human biological materials and genetic information. However, at the current time, the legislative will to implement such a measure does not appear to exist.

The example of benefit sharing in this report is consistent with the stated goal of the *Fundamental Principles* of making a significant contribution to the life and health of humanity and each individual, and to the welfare of society.[169] This gesture of goodwill may also go some way to overcoming some of the negative publicity and scepticism surrounding genetic research. Whether or not Kyushu University's pioneering commitment to benefit sharing will inspire other research projects remains to be seen.

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[164] *Ethical Guidelines*, Chapter 2. (Responsibilities *of Researchers, etc.*) (4) (*Responsibilities of the head of a research institution*), *Bylaw regarding the requisites for the personal information manager.*

[165] *Supra* note 4.

[166] *Supra* note 112.

[167] *Id.*

[168] *Ethical Guidelines*, *Enforcement, etc. of the Ethical Guidelines for Analytical Research on the Human Genome/ Genes,* (note 4).

[169] *Fundamental Principles*, Principle 24 (1).

The regulatory framework for the UK Biobank has been described as being "*at an early stage in its evolution*", with many areas lacking in detail.[170] This observation could perhaps just as easily be applied to the current Japanese regulatory provisions, where it seems that decisions on a number of sensitive ethical questions will made by individual Ethics Review Committees on a case-by-case basis. Stuart observes that further clarification of key issues of *data governance,* such as determining the scope of informed consent, the reuse of samples, the linking of samples to participants' medical records and the transfer of identifiable information to external organisations without anonymisation is likely to emerge from further dialogue between individual Ethics Review Committees and the Japanese Ministry of Health Labour and Welfare.[171]

At a broader social level, Stuart has observed that attitudes towards bioethics are currently in something of a transitional stage in Japan. Observers have pointed to the uneasy coexistence between American-influenced concepts of bioethics (with an emphasis on individual autonomy), and the more paternalistic, traditional Japanese concepts of ethics (*rinri*), which Masui and Takada summarise as being the understanding that "people in positions of responsibility possess knowledge which is correct, and we should be grateful when receiving the benefits of their wisdom."[172] Both the effectiveness of the current regime for the regulation of human biobanks in Japan and the continuing evolution of Japanese attitudes towards bioethics require close monitoring over the coming years.

APPENDIX I

Model Japanese Consent Form

Excerpt from the Ethical Guidelines for Analytical Research on the Human Genome/Genes, Issued by the Ministry of Education, Culture, Sports, Science and Technology, the Ministry of Health, Labour and Welfare and the Ministry of Economy, Trade and Industry, on March 29th 2001.

Chapter 3. Basic Attitude to Participants, (8) Informed Consent.

Bylaw Regarding the Contents of the Written Information for Informed Consent.

The written information given to the participant or his/her representative should in general include the following topics, which may vary depending on the nature of research:

1) That the donation of samples, etc. is voluntary.
2) That the person requested to donate samples, etc. may refuse the request without any penalty.

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[170] UK Biobank Ethics and Governance Framework: Summary of Comments on Version 1.0, May 2004. p.4

[171] *See* Stuart, *supra* note 8 *at* 7.10.5.

[172] Masui, T. *supra* note 5, p. 117 (*author's translation*).

3) That the participant or his/her representative may withdraw his/her informed consent at any time without penalty by expressing the intention of doing so in writing.

4) That with the participant's or his/her representative's withdrawal of informed consent, the samples, etc. donated by the participant and the research results concerning the participant will be destroyed unless they are unlinkably anonymised.

5) The reason for being selected as a participant.

6) The significance, purpose and procedures of the research (The target disease, analytical methods, etc. should be mentioned. If any, expected additions or alterations of the research plan should also be mentioned. If a disease such as a monogenic disease is targeted, the importance of the research, measures to be taken to prevent disadvantage to the participant, etc. and other issues peculiar to the disease should be mentioned.), and the research period.

7) In the case where it is difficult to obtain the participant's own informed consent, the importance of the research and the reason why the donation of samples, etc. by the participant is essential to the research.

8) The name and post of the chief researcher.

9) The expected outcomes of the research and the foreseeable risks or inconveniences to the participant, etc. (including inconveniences in social life such as social discrimination).

10) That the participant or his/her representative can, if so wishes, have access to, or have copies of, documents concerning the research plan and the research procedures to the extent that the confidentiality of personal information concerning the participant, etc. and the originality of the research may not be jeopardized.

11) Whether the samples, etc. donated and the genetic information derived from them will be anonymised linkably or unlinkably, and the concrete procedure of anonymisation. If anonymisation is not to be conducted, the fact with the reason for it.

12) Whether or not the samples, etc. donated or the genetic information derived from them will possibly be provided to an outside institution. If the samples, etc. or the genetic information will possibly be provided to an outside institution, that the Ethics Review Committee has approved the procedure of handling personal information, the outside institution to which the samples, etc. or the genetic information is to be provided, and the purpose of use of the samples, etc. or the genetic information at the outside institution.

13) In the case where part of the research is contracted out to a third party, the method of anonymisation, etc.

14) Matters related to disclosure of genetic information.

15) That the outcomes of the research may possibly produce intellectual property rights such patent rights in the future, and the party to whom such intellectual property rights will belong.

16) That the genetic information derived from samples, etc. may be presented in an anonymised form in academic meetings, etc.

17) The methods of preservation and use of samples, etc.

18) The method of preservation, use or destruction of samples, etc. after the research (including the possibility of being used for another research and the expected purpose, etc. of the research).

19) In the case where samples, etc. will possibly be provided to a human cell/gene/tissue bank for general research use, the academic significance of the bank, the name of the organization managing the bank, the method of anonymisation of the samples, etc. to be provided to the bank, and the name of the head of the bank.

20) Information about the use of genetic counselling (In the case where the participant has a disease such as monogenic disease, that genetic counselling is available to the participant, etc.).

21) The source of the research funds.

22) That provision of samples, etc. is gratuitous.

23) Information about participant relations such as the person or office to contact when the participant, etc. have questions, complaints, etc.

APPENDIX II

Proposed Model Consent Form for Participants in the UK Biobank

UK BIOBANK ETHICS AND GOVERNANCE FRAMEWORK

Version 1.0, 24 September 2003 (FOR COMMENT), p.9.

I. B. UNDERSTANDINGS AND CONSENT

1. Consent

Consent will be sought "to participate in UK Biobank". Participation will be cast as an opportunity to contribute information that in the long term may enhance other people's health. Because it will be impossible to anticipate all future research uses, strong governance and safeguards will be in place to protect participants' interests and the public interest.

Consent will be based on an explanation and the understanding of, amongst other things:

- the purpose of UK Biobank
- the fact that UK Biobank is not a healthcare programme but a research resource

- the kinds of information and samples that will be collected at enrolment, which may include data that some participants might consider especially sensitive
- the fact that there will be a link to the full medical record, past and ongoing
- the fact that UK Biobank will be the legal owner of the database and the sample collection, and that participants have no property rights in the samples
- the kinds of safeguards that will be maintained, including storage of data and samples in reversibly anonymised form, and severe restrictions on access to data and samples that are not anonymised
- the policy for making decisions on research access
- the assurance that only research uses that have been approved by both UK Biobank and an NHS Multi-centre Research Ethics Committee (MREC) will be allowed, and that data will be anonymised before being provided to research users
- the expectation that commercial entities will apply to use UK Biobank
- the possibility of being recontacted in future, by whom and for what purposes
- the need for UK Biobank to retain as many participants for as long as possible in order to maximise its value as a research resource
- the intention to continue to hold and allow research access to data after participants lose mental capacity or die, as such data are crucial for research resource
- the right to withdraw at any time without having to give a reason, and the meaning of withdrawal
- UK Biobank's commitment to maintaining active engagement with participants and society in general.

The points listed above are some elements of what it means "to participate in UK Biobank"; each is discussed in more detail later in the Framework. These elements and other customary undertakings will be addressed in particular information and the consent process.

UK Biobank will endeavour to make sure that participants understand what they are consenting to. Ways of doing this may be tested in an independent evaluation of the consent process used during the pilot phase.

The consent to participate in UK Biobank will apply throughout the lifetime of UK Biobank unless the participant withdraws. Further consent will be sought for any proposed activities that do not fall within the existing consent.