BIOETHICS CONSULTATIVE COMMITTEE

Ethical Consideration on Biobanking of Human Tissues

6/9/2011

Table of Contents

Ethical Consideration on Biobanking of Human Tissues

Introduction

The lack of knowledge on the molecular pathophysiology of human disease is the main stumbling block in effective and safe treatment option. Experience, especially the medical epidemiology one, has shown that the collection of bodily substances linked to the information on the donor's medical and socio-cultural background, has contributed in the identification of causative factors in disorders such as bladder tumours and aniline dyes or smoking and pulmonary cancer. Thus the organisation of a proper biobank is of utmost importance in the elucidation of human disorders.

This fact has been recognized by the world's major economies, and exemplified by the Organisation for Economic Cooperation and Development (OECD), that have stated that: 'biological resource centres are an essential part of the infrastructure underpinning life sciences and biotechnology . . . essential for R&D in the life sciences ….. and human health'. Furthermore OECD further specifies that the individual biobanks need to form 'a global network …..(that) is a critical element of the infrastructure'. The OECD definition of a Biobank[12] is "A collection of biological material and the associated data and information stored in an organised system, for a population or a large subset of a population." This definition brings out a number of considerations.

Biological Samples

For many years, laboratories and hospitals have collected and stored whole organs and tissues for diagnostic, therapeutic and research aims. The major source of this material was derived from the normal medical practice such as surgery, cytology, biopsies and birth products. Other sources would include gamete and embryo donations. Since the early 70's specialised biobanks have been initiated that targeted cells and their products (DNA, protein, etc.). Whilst the material that is donated for a specific medical purpose (organs and tissues transplants, assisted reproduction techniques, research with embryos and human foetuses) is usually regulated by specific legal regulations, collections that are donated for research are not so thoroughly regulated. Thus some form of ethical guidelines is required to safeguard both the donors and the curator's rights.

Several legal frameworks in relation to biobanks have been enacted. Of particular interest Recommendation No (92) 1 of the Council of Europe, *on the use of DNA analysis on the framework of criminal justice system*[6]*,* and *R (92) 3, on Genetic Testing and Screening for Health Care Purposes*[7], as both these recommendations consider biological samples and bodily tissues as *data carriers* (principle 8), and thus are regarded on the same level as automatically processed medical data, i.e. that wherein the biological samples do not constitute personal data, they inherently contain this kind of information, and thus can be "collected" through the appropriated analysis.

In 2003, UNESCO[15] adopted the first international legal tool that sets a number of rules about biological samples and the related personal data. A major issue that was established through this recommendation was that genetic data may contain information of unknown relevance at the time of collection. It also established the requirement for previous, free, informed and express consent from the concerned person when collecting such samples.

In view of this extensive history of utilising these collections, it might be a surprise that certain issues are now coming to the fore. The main reason for this is most probably the fact that with the deeper understanding of the human genome, the epidemiological research is increasingly internal (genetic predisposition) pathogenic factors. The ability of researchers to know one's "hidden" genetic past and future has been considered to be on a different level of knowledge identification as compared to the traditional knowledge which usually gives the "present" and "past" picture. It was thus felt that there is a need to produce ethical guidelines on this "new" biobanking activity.

Though some of these ethical considerations should be common for all the types of modern biobanks, certain types of biobanks might require some modifications to these ethical modifications. So it might be useful to give a short description on the different types of biobanks. Biobanks can be broadly divided either on the type of tissues stored (e.g. cells, DNA, Serum) or in accordance to the population being sampled (population based and disease specific) or ownership (Public or Private) or on the Purpose (research, forensic, etc).

Classification Based on Type of Tissue

Biobanks containing fixed tissue samples

These are similar to the pathological biobanks present in most of the World's hospitals. The banked tissue is usually derived from pathologically altered tissue and is usually fixed. Up to a few years ago, the available information from this tissue was limited to some genetic information related to the pathological state. With the advent of new molecular biology techniques and the ability to isolate single cells from the fixed tissue, both abnormal and normal DNA as well as RNA information is available. On the other hand, the information on the protein structure is severely limited and it is not possible to obtain living and thus reproducing cells from the fixed tissues.

DNA banks

Other biobanks contain genetic material (DNA), usually isolated from white blood cells, or from other donor tissue. DNA can be stored either as deep-frozen or as dry samples for a relatively long period of time. Apart from this they can also be utilised for a large number of analyses from which one is able to gain information on the whole genome of the individual.

Cell culture banks

In these Biobanks donor samples (usually blood cells but could also be any other living, nucleated cells) are transformed into permanent cell cultures. They are usually stored in very low freezing temperature (usually under liquid nitrogen) and thus, at least theoretically, constitute an inexhaustible source of DNA of almost unlimited durability. They can also be utilised to study gene function, expression and cellular functions.

Classification Based on Population

Population Based Biobanks

A population based biobank is best defined as a large repository of donated human tissue (more commonly fresh but could also be fixed) form which cells, DNA and other cellular components can be harvested and stored together with personal information that is collected from volunteers with and without disease. Examples of such biobanks are the National Population Based Biobanks around the world.

Disease Based Biobanks

Disease based biobanks are repositories for tissues and cellular material derived from a volunteer population that have a particular condition. These are usually smaller the population based biobanks and are usually collected for the study of a specific disease.

Classification Based Ownership

Public Ownership

These biobanks are either directly owned by the Government or else have been set up in partnership with the government. These biobanks would include biobanks within state hospitals and academic institutions.

Private Ownership

These are any biobanks that are owned by academic and medical institutions and hospitals that are not directly under the control of the government. They would also include biobanks that belong to biotechnology and pharmaceutical companies and biobank storage companies. These private biobanks offer major ethical questions as they are more difficult to monitor.

Classification based on Purpose

Research

These are biobanks that have been set up with the principal aim of utilising the samples and information for research purposes.

Forensic

These collections include specimens that are usually collected during a criminal investigation and consist of DNA and DNA fingerprinting data.

Transplantation

These biobanks are usually set up for the purpose of collecting living donor cells that can, later on be utilised in transplantation procedures. The most common of these are the cord blood stem cell biobanks that store blood stem cells from cord blood at birth, to be utilised in bone marrow transplantation.

Diagnostics

A diagnostic biobank is a collection of biological material from human beings which is given for the purpose of medical examination, diagnosis and treatment. These are the typical biobanks that one finds within the pathology laboratories in hospitals.

For the purpose of this paper, the only biobanks that shall be taken in consideration are those that are utilised for research purpose as the other three are strictly regulated by legislation.

Ethical Aspects

The sequencing of the human genome in conjunction with new sequencing and analytical technologies has opened up new horizons for the use of tissues in research. The possibility of extracting genetic information from various tissues has put in the forefront the need to have clear ethical guidelines on the protection of the individual.

The most important ethical consideration in relationship to Biobanks for research purposes

- Informed consent of the donor
- Data Protection and the right to anonymity of samples and data
- Secondary use of stored tissue
- Donor remuneration, Commercialisation and ownership of the stored tissue
- Individual or social discrimination based on knowledge derived from the study of the samples in the biobank

Informed consent of the donor

Informed consent has become a universally acceptable principle. Informed consent implies that the person has the “capacity to give consent.” Though different legal systems define the “capacity to give consent” in different formats the basic criteria presuppose that an individual is capable to give consent when s/he has the ability to:

- to understand the purposes, nature, significance and implications of the measure calling for consent,

- believe that information;
- to weigh the pros and cons and
- to exercise the right of self-determination in the light of the understanding arrived at.

In contrast to its use and definition, there is no single consensus on its method of application. Thus it maybe explicit (opt-in) or implicit (opt-out), and depending on the nature of the information to be given to the patient of a generic or specific (a request for a generic use for any research, or for a particular research or for a type of research or for the permission to obtain the consent at a subsequent moment when the research aims become more concrete). Though the recommendation of the Council of Europe Rec(2006)4 of the Committee of Ministers to member states on research on biological materials of human origin,[4] adopted on the 15 March 2006, recommends that "*Information and consent or authorisation to obtain such materials should be as specific as possible with regard to any foreseen research uses and the choices available in that respect,"* there is no consensus amongst European countries. Some countries take a very restrictive approach where each donor has to be consulted and a new consent obtained for each new individual research project that shall use that tissue. This is the present situation in Sweden for non-anonymized samples. The other extreme for the opt-in consent is a general consent for the use of the tissues in various research projects though each research project has to obtain the approval of a research ethics committee for the use of the samples. In the Maltese case, most of the ethics committee's decisions have favoured an approach that seems to be a balance between these two extremes. In most of the research projects the consent form gives the donor the ability to identify whether the tissues shall be used solely for the research in question or whether it could also be used for other research projects. In this way, wherein the donor is given the opportunity to freely choose the type of consent, removes the need for the individual researcher to ask the donor for consent every time the tissue is used for a research project.

The implicit case, considers that consent has been given by the donor for the use of the tissues in research as long as the donor does not explicitly express a desire to have his tissues removed from the study. This is the system that is utilised in The Netherlands[13] for anonymous tissues and is the line that has been followed in Malta for the National Newborn Cord Blood DNA bank that is a fully anonymized bank.

Data Protection

As has already been defined, a Biobank is a collection of biological material and the corresponding personal data of the donor. The ability to trace back the identity the donor is evidently an issue where the samples are not anonymized but it might be less evident that this traceability can also be an issue in certain specific biobanks e.g. special rare-disease biobanks in small communities where the numbers are so small that the individual might be identifiable with a very small number of data points (such as age and gender).

There are various methods by which the data can be coded. This includes:

- Direct identification
- Coded
- Encrypted
- Anonymized
- Anonymous

In the case of the direct identification, any researcher that has access to the data can identify the donor. When the personal data is coded, the identifiable data is physically separated from the personal data and the sample, but the procurer of the sample (usually the caring physician) has access to the code and thus can identify the donor. When data is encrypted, third party persons transform the code into a number of characters. Thus the aid of these third parties is required to retrace the donor. When the identifying code is anonymized, the connection between the code and the identifiable data is completely lost and thus the ability to identify the donor is lost. In the case of anonymous samples, the samples were donated in a completely anonymous form, and thus the personal data of the donor have never been known.

In general, in the context of biobank, data protection is synonymous with access control of stored data and the licit use of the data. Obviously, complete protection is only achieved through full anonymization but this loses the ability for the researcher to pass on important data to the donor, especially if the latter wishes so. Thus wherein anonymization might be socially easier to be accepted, it limits the research benefits to the community as compared to the individual. Thus the setting up of a secure data storage system with proper encryption protocols, access control and logging system is a requirement for all biobanks that are neither anonymized nor anonymous. It has also to be noted that "even when full consent has been given, particular studies may use the material at different levels of anonymization."[7]

When there is a research need for both samples and data to be connected (this is the case for most biobanks) then the best solution might be to either code or better still encrypt the data. In the personal experience of the writer, all the biobanking activity that has been authorized in Malta, the system that has been utilised to safeguard privacy is one of encryption, with the code breaking data being kept by a third person – usually a senior scientist not directly involved in the research.

There is another interesting aspect that is related to consent. Once research data has been obtained from a sample that was obtained with a proper consent, can the donor ask for the data to be destroyed? In this are one has to balance the rights of the donor with the rights of the researcher. While the donor has voluntarily donated the sample with an informed consent, the researcher has utilised funds and time to obtain the research data. In addition, this data is useful to the community and other individuals with the disease. Cambon-Thomson[3] (2004) proposes "that when scientific data have been produced with the consent of a person, this person should not have the right to ask for their destruction, but only for their anonymization."

Secondary Use of Stored Tissues

One of the main problems facing the curators of biobanks is the ability to use the tissues for a research proposal that was not anticipated for when the tissues were originally harvested. In most of these cases the donors were not informed on the possible future use of the donated samples and thus there was no consent. Wherein in an ideal situation all the research on archival material should have had prior consent for that study, in actual fact in most cases one would have to wait for decades to collect the necessary number of samples[5]. Similarly to the informed consent situation, though the Council of Europe[4] recommends that "Biological materials removed for purposes other than storage for research should only be made available for research activities with appropriate consent or authorisation," there is as yet no consensual agreement on this ethical issue. Some ethical boards have taken a very rigid approach where no studies can be undertaken on archival material unless prior consent has been obtained to more flexible approach where the decision taken is based on the traceability or otherwise of the person, the possible anticipated use as compared to the original use, the risk implications of the research on the individual and the type of consent at the time of collection. A common thread throughout all these approaches (and in agreement with the Council of Europe recommendation, is that there is a need for an approval from an independent committee. In the case of Malta, this situation has as yet never been discussed nor have any decisions ever been taken on the ethical issues surrounding the secondary use of archival material. A possible way forward and that is favoured by the majority of ethical reports and opinions, is that no prior consent is required to use these samples as long as the sample data is coded or anonymized and if this is not practical or useful, to ask the proper consent from the donor. The probable financing of the EU Biobanking and Biomolecular Resources Research Infrastructure, that has, as one of its aim to produce a common legal and ethical framework, can assist European biobanks to work together and share tissue and personal data with ease.

Commercialisation of the stored biological tissue

The European Group on Ethics, in its 1998 opinion on The Ethical Aspects of Tissue Banking, stated that "All Member States of the European Union adhere to the principle that donations of human tissues must be free, following the example of blood, and this rules out any payment to the donor." This approach was also taken by the Council of Europe. Similar to blood donations, the only compensation that the donor may receive are those to cover the constraints associated with the tissue removal such as travel expenses and loss of earnings. Though arguments exists that for fairness sake, when the tissue sample is or has the potential of being a source of profit than the donors should be paid as this might also increase the supply of tissues. On the other hand, there are valid prevailing arguments that consider the donation as an altruistic act akin to organ donation. These arguments are inspired by the fact that the human person should not be considered an object and as a safeguard against the exploitation of the underprivileged, who might be lured to donate primarily for financial reasons.

Another aspect is the commercialization of processed human tissues for therapeutic use. For a number of workers in the field, the altruistic arguments that argue in favour of no compensation to the donor are basis upon which they argue in favour of non-profit-making biobanks. On the other hand, and in a similar fashion to blood derivatives, there are valid arguments that the processing and conversion of these tissues to render them therapeutically active, involves costs that should justify the commercial sale. In addition, industry requires profit so as to invest in certain areas.

Integrated within the discussion of commercialization and profits are the ethical questions concerning ownership, benefit sharing and return of results. These have elicited various debates and proposals[10,2]. Though the general practice is that the information generated from studies on donated tissues belongs to the researcher or team that creates it and that the individual who may have been a subject of the research has no legal entitlements to that research, this view is by far not universal especially across the Atlantic. This typified by the statement issued out by the American Society of Human Genetics[1] (ASHG) that established that 'banked DNA is the property of the depositor unless otherwise stipulated'. In contrast, the British MRC Working Group[11] on Collections of Human Tissue and Biological Samples for Use in Research was of the opinion that it is the funding body that retains ownership of the collection with the researcher being its custodian. Wherein the custodian has the responsibility of control of the access to the collection, the funding body has to determine the purpose of the collection and if it is available to commercial or academic researchers or both. Finally, the potential donors should only give their consent once informed about who owns the sample and its subsequent use.

The issue of ownership is most controversial in connection with the patentability of 'inventions' derived from the scientific analysis of human material and this is strongly contested amongst various nations and particular groups.

On an international level, there is a large consensus on the unpatentability of human tissue. This position has been maintained by HUGO[8,9], by the Council of Europe's recommendation on the Protection and Patentability of Material of Human Origin[14] ('human beings are subjects – not objects – of law'.) and by the European Commission Directive[6] concerning the Legal Protection of Biotechnology Inventions intended to complement international intellectual property provisions ('an element of the human body in its natural environment or even a sequence or partial sequence is unpatentable' and that 'even a patentable invention – according to the European patent law – can be excluded if contrary to public order and morality').

Protection from Genetic Discrimination and Stigmatisation

Genetic discrimination

The utilization of knowledge of a person's genetic characters as a justification for unequal treatment is considered to be discrimination. This is particularly so when applied to employment and insurance

contracts. This risk is increased as more knowledge is amassed about genetic dispositions and in particular where large volumes of data are assembled, as in biobanks. This apprehension needs to be addressed by adequate legislation as well as ethical guidelines. Such legislation should include the adequate coding of personalized data, secure access and logging, a restriction of the purpose for which the data may be used together with a legal ban on access for non-research purposes and confidentiality requirements. Once adequate regulations and protocols are in place, the risk of unauthorised access to data is in fact much lower in the case of biobanks (all data is usually coded) than for routine clinical data (by its nature, clinical data is hardly encrypted).

Genetic stigmatisation

Wherein the risk of discrimination can be easily avoided through regulation, responding towards the risk of stigmatisation is more difficult. This is because stigmatisation is mainly a problem of perception by others or self. Once the disease causing genes are identified, it becomes easy to identify carriers. Population based studies to identify the incidence of the disease, could also result in the knowledge that members of an ethnic group are at a higher risk of the genetic disease (e.g. Tay-Sachs disease in Ashkenazi Jews, Thalassaemia and Familial Mediterranean Fever in persons of Mediterranean descent). Thus these individuals might be classified or marked and thus stigmatisation might result.

Another aspect is the impact on the donor's relatives of any identification of genetic disease. Wherein the donor is protected by proper consent guidelines, relatives and even entire groups of people, who have no previous knowledge of the genetic disease, might find themselves the recipient of this information and may not wish to possess it. The question is whether third parties who might possibly be affected ought to be consulted when consent is given for donation to a biobank. The counterargument for this line of thought is the right of those directly affected to self-determine in relation to their own bodies and personalities. The later right takes precedence over the collective right.

Samples and data of those incapable of giving their consent and of deceased individuals

Incapacity for consent

As has already been described in a previous section, Informed consent implies that the donor has the relevant capacity to give this consent. In view of its definition, the capacity to give consent might be lacking due to age (children and adolescents), disability or disease (dementia) or accident. As for other instances in medical practice, the decisions on behalf such individuals have to be made by the legal representative of the individual. Thus in the case of minors, it is usually their custodians while for adults it would be their legally authorized representative. Though lacking the capacity to give consent, they still have a right for the information, including information on the use of their samples, data generated and on any scientific findings arising from the study. Another important aspect of the consent is that the legal

representative should take into account the wishes of the person and constraints on sample donation must be shown if the person shows any signs of refusal. In accordance to the principle of the "right not to know," genetic information that has no direct therapeutic or diagnostic relevance to the person concerned should not be divulged to persons that lack the capacity to give consent.

The debate whether research on subject lacking the capacity to consent is a hotly debated issue. Wherein there is agreement on research that would benefit the donor, there is disagreement on research that would benefit others rather than the donor. The decision whether a research is legitimate or not should hinge on the level of risk that the donor is exposed by accepting to be part of the research. If the risk is minimal or non-existent (e.g. blood sample, urine sample, saliva sample) than it should be considered as legitimate, especially if the research concerned is intended to benefit others affected by the same disease or (in the case of children) persons in the same age group. On the other hand, when the risk is non-minimal (both physical and psychological) then restraint has to be shown and the subjects should not be exposed to that risk. These principles should not be applied if the procedure is part of a therapeutic or diagnostic procedure, as long as the protective procedures for confidentiality described previously are followed. What is clear is the need for verifiable criteria and methods that can utilised towards the objective definition of minimal risks.

Deceased persons

Tissues and samples from deceased subjects, whether stored in medical (pathological) banks or whether purposely collected during post-mortem examinations, maybe extremely useful for medical research. In this case the same criteria as for those that are incapable of giving informed consent should apply, as long as the deceased had not given his/her consent during his/her lifetime. In a similar way, wherein the next of kin can furnish the consent for use, the wishes of the deceased that were expressed during his lifetime should be taken into account.

Transitional solutions for "old" collections

Finally, one should also consider the research use of "old" collections i.e. collections of samples that were originally taken for diagnostic or therapeutic reasons, where obtaining the subject's consent is impossible. As these might have been taken in an era where the awareness of the importance of personal rights was lacking, judging them by present day criteria could be a disservice towards scientific discovery. In general, as the samples would have been taken considerable time before their use, there is minimal chance that the subjects would be personally affected by the research. Additional protection would be provided by the fact that an ethics board approval is always required and that samples and data is kept confidential.

Access to biobanks

Where biobanks are publicly funded (but this can also be legally promulgated to private biobanks) it is in the public interest, and thus indirectly to the donor, that the information that can be garnered through the use of the samples should be available to as many interested researches as possible. One possible solution to encourage the transfer of information whilst safeguarding the resource and thus facilitate harmonisation and collaboration, would be the creation of a “safe” and “trusted” third party to be used for all researchers as a trustee for the names, identity and samples of participants[17,16]. the European Union BBMRI initiative have proposed the setting up of regional hubs that would follow common legal, ethical and testing protocol, that would be responsible for the acceptance of samples from the other participating banks and then transfer the data to third parties in accordance with accepted protocols. This would offer a reasonable protection to the owners of the bank, act as an information buffer between the bank and the researchers (thus offering an extra protection on personal data protection aspects) while still openly sharing the required data.

Conclusion

The importance of biobanks in the study of human disorders has seen an exponential increase in the past two decades and the prospects are that these shall keep on increasing as further studies are conducted on more complex and multifactorial conditions. It is thus not surprising that they also raise a large number of legal and ethical issues that require a deep understanding and a sense of balance between the individual’s and the community’s rights. These issues require to be re-assessed as new technologies come into the market and as new discoveries are made. A multidisciplinary approach that engages academic scientists (including the social and human sciences, the medical sector, the economical sector and society at large, is required so as to obtain the best balance within a sustainable development scenario.

Bibliography

1. American Society of Human Genetics DNA banking and DNA analysis: points to consider. Ad Hoc Committee on DNA Technology, American Society of Human Genetics Am.J.Hum.Genet. 42(5) 1988 .

2. Ashcroft, R. The ethics of reusing archived tissue for research Neuropathol.Appl.Neurobiol. 26(5) 2000 .

3. Cambon-Thomsen, A. The social and ethical issues of post-genomic human biobanks Nat.Rev.Genet. 5(11) 2004 .

4. Committee of Ministers, Council of Europe Recommendation Rec(2006)4 of the Committee of Ministers to member states on research on biological materials of human origin 2006 .

5. Council of Europe Steering Committee on Bioethics Draft explanatory report to the draft instrument on the use of archived human biological materials in biomedical research 6 2002 .

6. European Parliament and Council Directive On the Legal Protection of Biotechnological Inventions. 98/44/EC 6-7-1998 .

7. Hair, J. F., McNicol, A. M., and Gusterson, B. A. Is research on human tissues at a crossroads? Eur.J.Cancer 39(16) 2003 .

8. Human Genome Organisation Position statement on cDNAs: Patents 6-1-1992 London.

9. Human Genome Organisation Statement on patenting of DNA sequences 2000 .

10. Human Genome Organisation Statement on the principled conduct of genetics research of the Human Genome Organisation. Statement approved by HUGO Council on 21 March 1996, Heidelberg, Germany Law Hum.Genome Rev. (12) 2000 .

11. Medical Research Council Human Tissue and Biological Samples for Use in Research, Operational and Ethical Guidelines 4-5-2001 London, UK.

12. OECD Creation and Governance of Human Genetic Research Databases 2006 Paris.

13. Oosterhuis, J. W., Coebergh, J. W., and van Veen, E. B. Tumour banks: well-guarded treasures in the interest of patients Nat.Rev.Cancer 3(1) 2003 .

14. Parliamentary Assembly Council of Europe On the Protection and Patentability of Material of Human origin Recommendation 1240 (1994) 14-4-1994 .

15. UNESCO International Declaration on Human Genetic Data 2003 Paris.

16. Zika, E., Paci, D., Braun, A., RijKers-Defrasne, S., Deschenes, M., Fortier, I., Laage-Hellman, J., Scerri, C. A., and Ibarreta, D. A European Survey on Biobanks: Trends and Issues Public Health Genomics (Epub ahead of print) 15-4-2010 .

17. Zika, E., Paci, D., Schulte in den Bäumen, T., Braun, A., RijKers-Defrasne, S., Deschênes, M, Fortier, I., Laage-Hellman, J., Scerri, C. A., and Ibarreta, D. Biobanks in Europe: Prospects for Harmonisation and Networking 2010 Luxembourg.