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The problem of informed consent content for genetic research using biospecimens stored in biobanks#

O problema de conteúdo do termo de consentimento esclarecido na pesquisa genética usando bioespecimens armazenados em biobanks

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ABSTRACT: This article exposes the difficulties associated with informed consent content for genetic research when using biological materials stored in Biobanks. Comprehension of disclosed information may be complicated, particularly in vulnerable populations. Differences in understanding and perception of risks may affect consent. Legal safeguards and enhancement of informed consent procedures must be placed so that Biobanks will not be used in any way that may harm the individual who has provided the sample or her genetic relatives or community.

KEYWORDS: Genetic Research. Informed Consent. Vulnerable Populations.

RESUMO: Este artigo expõe as dificuldades associadas com o conteúdo dos termos de consentimento esclarecido da pesquisa genética usando materiais biológicos armazenados em Biobanks. A compreensão das informações reveladas pode ser complicada, em particular em populações vulneráveis. As diferenças na compreensão e percepção de riscos podem afetar o consentimento. Salvaguardas legais e o aumento de procedimentos de consentimento esclarecido devem ser oferecidos para que os Biobanks não sejam usados de nenhuma maneira capaz de prejudicar o indivíduo que forneceu a amostra ou os seus parentes genéticos ou a comunidade.

PALAVRAS-CHAVE: Pesquisa em Genética. Consentimento Livre e Esclarecido. Populações Vulneráveis.

INTRODUCTION

A broad definition of Biobank is that of being a repository of biological tissues[1,2,3,4]. Samples may derive from clinical setting, research projects or judiciary mandate and may come from surgery, wastes, diagnosis tests, birth products (placenta and umbilical cord), body parts of deceased people, donation of gametes or embryos or biological materials from genetic research population studies. Data associated to the samples may be individual (clinical, life style), familial (genealogy information or ethnic origin) or belonging to a group (geographical location, language). Biobanks storing human biological materials (biospecimens) are a help specifically for health and research purposes and may be useful in translating advances in genomics or genomic population research into knowledge of direct clinical and public health relevance[5,6,7], but their use have raised numerous ethical and legal issues[8,9,10]. There are strong arguments to protect the interests of tissue donors because of concerns with invasion of privacy, the difficulty to guarantee confidentiality, the possibility for discrimination and stigmatization of individuals, ethnic groups and populations, and because of ownership issues and discrepancies in commercial use of biospecimens[11,12,13,14,15]. Genetic research can be done in linkage studies to identify gene sequences associated with inherited diseases, association studies to find correlations between diseases and genetic changes, genetic epidemiology to study interaction of genes with environment and pharmacogenetic studies to study genetic basis of interaction of human body with drugs. Each of these types of studies uses genetic databases in a different way and may raise different legal, ethical and social issues.

Advances in biotechnology and bioinformatics have made possible to store in huge scale biospecimens and data and due to globalization interest, trans-national sharing of biobank resources has increased. There are collaborative genetic research projects focusing on diseases prevalent in developing countries which require shipment of samples stored in biobanks from developing to developed countries. Therefore, there is a growing need to harmonize biobank processes. Legal safeguards must be placed so that biobanks will not be used in any way that may harm the individual who has provided the sample or his genetic relatives or community.

INTERNATIONAL GUIDANCE

In light of the legal and socioeconomic issues related to genetic research and the use of stored samples, international guidelines have been proposed. The UNESCO *Universal Declaration on Bioethics and Human Rights* pro-

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vides broad guidance on consent, privacy and sharing of benefits. The UNESCO *Universal Declaration on the Human Genome and Human Rights* (1997) has provisions relating to the status of the human genome as the common heritage of humanity and examines the fundamental rights of the individual and society that should be protected during research, but deals only with the human gene in its natural state and not with assemblages of data in biobanks. The International Declaration on human genetic data elaborated by UNESCO (2003) settles a number of rules about biological samples and on personal data which may be collected from those samples; it establishes that genetic data may contain information of unknown relevance in the moment of the collection of the biological samples and that genetic data may be culturally important for individuals or groups of people. It also states the requirements which have to be met to use biological samples preserved when genetic data are to be collected: previous, free, informed and express consent from the concerned person is required. The World Medical Association Declaration of Helsinki, *'Ethical Principles for Medical Research Involving Human Subjects'* (1964, last revision 2008) provides guidance to physicians and other participants in medical research involving human subjects, including research on identifiable human material or identifiable data. The Council for International Organizations of Medical Sciences (CIOMS) in its International Ethical Guidelines for Biomedical Research Involving Human Subjects (2002) contains guidelines for implementation of informed consent when biological materials are extracted for research. The Council of Europe, *'Convention on Human Rights and Biomedicine'* (1997) deals primarily with protection, especially of human rights, in the context of the application of biology and medicine. The Council of Europe also adopted the *'Recommendation Rec2006(4) of the Committee of Ministers to member states on research on biological materials of human origin'* (2006) which applies to research activities in the health field involving the removal of biological material of human origin to be stored for research use. Within this recommendation, there is also a brief section on population biobanks. The HUGO Ethics Committee, *'Statement on Human Genomic Databases'* (2002), provides principles and recommendations for biobanks generally. The Organisation for Economic Co-operation and Development, in its *'OECD Guidelines on Human Biobanks and Genetic Research Databases'* (2009), provides principles and best practices for the establishment and management of human biobanks. The Organization for Economic Co-operation and Development document named *'Best Practice Guidelines for Biological Resource Centres'* (2007) provides guidelines for the establishment and management of access, use and security of samples and data. The International Society for Biological and Environmental Repositories document *'2008 Best Practices for Repositories: Collection, Storage, Retrieval and Distribution of Biological Materials for Research'* provides best practices for the management of all aspects of biobanks.

Developed countries have come with regulations to address the issues[a]. Of importance is also to standardize the quality of biospecimens in storage condition for use in research in an efficient way, for which efforts have been made to establish guidance[b]. On the other hand, most Latin American countries lack specific national regulations for the use of stored human samples.

INFORMED CONSENT CONTENT FOR PERFORMING GENETIC RESEARCH WITH BIOSPECIMENS STORED IN BIOBANKS

Research ethics has established the right of participants to be fully informed of objectives and procedures of research projects and the right to withdraw from that project at any time. This does not fit completely with goals of biobanks, who may have open-ended scientific goals; neither may fit logistic difficulties in some cases, like recontacting people whose biological material and related data are stored in biobanks every time a new research project intends to make use of their samples[16,17,18]. Also, the populational logic of some Biobanks make difficult to report individual health related data due to privacy protection or because of the requirement to anonymize data[19]. Ethical concerns also arise regarding consent for future use with children and with those who are incompetent[20,21].

a. i.e, the U.S.: NIH Office of Protection from Research Risks, 1993; Data protection Act, 1998; CCNE, 2003; Genetic Information Nondiscrimination Act (GINA), 2008; DHHS 45 CFR Part 46; OHRP: http://www.hhs.gov/ohrp/humansubjects/index.html

b. National Cancer Institute NCI Best Practices for Biospecimen Resources, 2007; Good Laboratory Practices GLP: http://www.oecd.org/document/63/0,2340,en_2649_34381_2346175_1_1_1_1,00.html; Clinical Laboratory Improvement Amendment: http://wwwn.cdc.gov/clia/; U.S. Food and Drug Administration FDA Quality System Regulation, 21 CFR 820: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm?cfrpart=820

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The recommendations of international regulations on the necessary content of informed consent and skills are complex to perform:

Communication: The information to be provided to potential participants needs to be clear and in simple language, concise and explicit. Communication strategies should take into consideration the different needs of the participants, employing different formats and modes for providing information to participants. Policy and procedures for ongoing communication with participants and information for contacting the biobank should be given.

Scope of the information: During the informed consent process, researchers should provide potential participants with sufficient information on the nature, implications, foreseeable risks and benefits of their participation, so that they can realistically assess the implications and can make an informed decision; particularly, risk of psychosocial harms, such as potential stigmatization, discrimination or intrafamilial conflicts, and the possibility that research may create or increment the risk of stigmatization or discrimination of groups must be informed.

Intended purpose: The purposes for which data will be used and/or disclosed must be informed.

Ownership: clarification of ownership issues with respect to biospecimens, information and collection.

Source: the source of biospecimens that will be collected for research; for example, whether the biospecimen will come from leftover tissue from a surgical procedure or from an additional procedure, for example an extra blood draw.

Reconsent: circumstances in which reconsent might need to be sought and/or in which a waiver of consent may be sought.

Consent of children: whether child participants will be involved and whether, when and how a child's assent will be obtained.

Culture respect: the consent process should take into consideration the cultural sensitivities of the community in which the research is to be conducted as well as the participant's cultural and/or religious beliefs.

Contact / recontact: whether information from or about family members, in addition to that provided by participants, is required for the research; whether participants will be re-contacted in the future (option given), the circumstances in which re-contact will be permitted and the conditions that will govern re-contact.

Data storage, transfer and disposal: the form in which data will be stored (identifiable, re-identifiable, non-identifiable); duration of storage, transfer and disposal procedures, including for international transfer of data where applicable.

Confidentiality and privacy: procedures and safeguards used to protect confidentiality and privacy, who will be the custodian of the biospecimens and what will be the custodian's role; details of data linkage, including which health and other records are to be accessed.

Release of information: whether the research may reveal information of potential importance to the future health of participants or their blood relatives; whether or not individual or aggregate research results will be released to the participant and/or his or her family or health care provider respecting the right to know the information and the right not to know it when there is no therapy.

Access: whether biospecimens and genetic information will be made available for non-research purposes such as proficiency testing; the possibility of sharing biospecimens and data with commercial entities, including those from other countries, and the publication of data and its availability on the Web; the policy with regard to access to biospecimens and data by third parties such as insurers, employers or law enforcement agencies.

Commercialization and benefit sharing: potential commercialization and whether participants will derive benefit from any such commercialization; policies with respect to the sharing of benefits from the research must be included.

Right to withdraw: the right to withdraw, the available types of withdrawal, the implications of such withdrawal, and whether it will be possible to withdraw biospecimens and data; patients have the right to refuse biospecimen donation, and this will in no way influence their treatment or eligibility to participate in clinical trials.

Death or incapacity of participants: arrangements regarding biospecimens and data in the event of incapacity or death of participants.

Waiver of consent: a human research ethics committee may waive the requirement for consent if: there is minimal risk to human subjects, when the waiver will not "adversely affect the rights and welfare of the subjects"; there is no known or likely reason for thinking that participants would not have consented if they had been

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asked; there is sufficient protection of their privacy; there is an adequate plan to protect data confidentiality.

The possibility of tracing the person from whom sample and data were derived varies according to how the samples are linked to their donor identity in the database. Samples and associated information can be[22]:

Identifiable: The identity (or personal and unique id number) of individuals is directly attached or linked to the samples or data.

Traceable or coded: A code is attached to them and the correspondence between code and identity is physically separated from sample and data. A limited number of people can connect the code to the identity.

Encrypted: There is a further level of protection through encryption (that is, the code is transformed into several characters that are linked to the code with the intervention of a third party). This third party intervention will then be required to trace individual identity.

Anonymized: The link has been irreversibly cut between sample/data and the individual identity.

Anonymous: There has never been any possibility to link the sample and the attached data to a given person.

The principle that an individual should have some say over whether and how their biological material is used is widely recognized within research fields and the wider community, but is interpreted in a variety of ways. In many industrialized countries there is opposition of civil society to the creation of genomic databases because of concerns about the unique nature of genetic information and the resulting implications for privacy, surveillance, discrimination, and commercialization. Also personal religious and cultural beliefs must be respected.

RISK PERCEPTION

True consent requires full understanding of risks and benefits involved in research and perception of risks in the informed consent process affects the acceptance of research. Potential risks of genomic research are mainly of socioeconomic nature, which may affect not only individuals but families and ethnic groups as well. Comprehension of disclosed information in informed consent processes may be complicated in low literacy groups and in elderly with lack of education in science.

Often civil society has limited exposure to what is going on in research, depending on what media covers about the issue, so that they do not have an understanding of the vision of all stakeholders involved. Particular groups may have a negative reaction against participating in research by donating their tissues if they focus on fears of stigmatization and discrimination exposed by media. Other groups may have a positive reaction to participate in research focusing on expectations of finding new therapeutic approaches. The process of obtaining informed consent may be too difficult to explain by reading an informational brochure to vulnerable populations since there are many issues involved as reflected in international guidelines. Vulnerable groups may respond based on their little knowledge and understanding and not because of having reflected in the issue.

There is a wide debate over several interrelated legal issues in biobanking: 1) Ownership of biological materials; 2) privacy concerns raised by the difficulty of accepting that biological samples must be completely anonymous without incurring into the practical impossibility of exploiting their information potential, since biological and genetic data retain such potential only if they can be traced to the evolving clinical history of the original donor; 3) content of the donor's "informed consent", as a tool which may serve to protect donors privacy, research interests and functioning of the biobank; broad consent for example is not truly informed consent, but rather a generic authorization that sacrifices the right of the donor to self-determination in favor of research interests[23,24,25]; 4) intellectual Property issues and the patentability of biological samples and the protection of databases storing genetic information obtained from the samples.

LATIN AMERICAN BIOBANKS

Currently most biobanks in Latin America function with their own norms of consent and quality standards for use of human biological materials in research in the absence of specific country regulations. These norms may be too open or too restrictive for research subjects or researchers satisfaction. There are numerous bioethical issues to take into account in order to satisfy research needs and guaranty data protection of human subjects from which specimens are taken. Issues of privacy and

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safeguard of confidentially and differences in understanding and perception of risks are culturally determined[26]. Personal identifiers or community/population identifiers may cause problems in safeguarding confidentiality over sensible issues which risk the possibility of social stigmatization or discrimination. Anonymity of the samples may not preclude the possibility to trace the community or population origin if the location, language or name of the ethnic group is given. Moreover, depending on the type of research some health and environmental exposure data may be necessary to keep. Furthermore, archive samples may be used without previous consent of donor.

In developed countries, there are reports on the views of sample donors with respect to future genetic research with store samples[27]. Such views have not been reported in the public domain in Latin America. Currently is not known how genomic research demands in relation to health are perceived by Latin American populations.

Consent to collect biospecimens from indigenous groups is a sensible issue due to their vulnerability and the value associated to body parts in many of them. Also there is generally a requirement to ask consent previously to elderly leaders. Several declarations of indigenous populations in Latin America pronounce against the collection of blood samples by diversity projects of the human genome project to characterize their DNA[28]. In Chile research with blood samples taken from mapuches caused a protest by leaders who were not consulted[29]. In a study carried out by our group it was shown that lack of knowledge about the technology and implications of genetic research is associated with an increase in anxiety and hostility towards genetic experimentation in Latin America and that civil society relies on media coverage for their knowledge[30]. In Mexico, the National Institute of Genomic Medicine, first of its kind in Latin America, was created to map the genome of Mexicans in order to promote preventive medicine, but since its inception it has provoked social controversies in misunderstanding its purpose[31,32].

CONCLUSION

While the interest in the use of international biospecimens for genetic research has increased considerably, there are still many unresolved issues over how to handle informed consent content and enhance understanding of risks and benefits for donated samples, particularly for vulnerable populations.

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