Guidelines for Genetic Biobanks

Italian Society of Human Genetics

Working Group: "Genetic Biobanks"

Telethon Foundation

Research Services

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SUMMARY

INTRODUCTION

The rapid advance of genetic research and applied technologies has led to a considerable increase in interest in collections of human biological material. Collection of tissue samples and cell lines from which nucleic acids and proteins are obtained are called genetic biobanks and represent an important resource for diagnosis and for research, from basic research to treatment of genetic diseases.

The success of research into the identification of disease genes, susceptibility genes and possible therapeutic applications, including the development of new and specific pharmaceuticals, depends on the availability of biological samples from affected persons or carriers, or those predisposed to genetically-caused pathologies, or who manifest variability in their response to pharmaceuticals. Numerous biobanks have been created around the world, thanks to donations from patients and their families, who have participated and continue to participate generously in research development.

The "gene" has become a precious resource and it is important to ensure that the establishment of DNA biobanks around the world does not result in solely an economic gain to the disadvantage of the interests of patients and of society, limiting the role of public research. In fact, this risk exists because the public laboratories that have biobanks may find it necessary to give precious genetic material to the pharmaceutical industry in exchange for funding, either to strengthen research means or to maintain the biobank. Exclusive contracts for use of biobanks, proposed by some businesses, can be disadvantageous for public laboratories, which risk becoming mere distributors of DNA, as well as for the diversity and independence of research. Moreover, we are witnessing a new form of "scientific colonialism", specifically in developing countries where there are genetically-isolated family groups, families of large numbers, and strong consanguinity. In fact, some public and private laboratories, although in limited numbers, attempt to secure access to samples from the patients and their families without providing them the necessary information about the biobank and potential commercial use of the DNA. Norms governing the protection of privacy and the obligation to obtain consent for the banking of samples for research purposes are severely lacking in some countries.

Finally, there are numerous collections of biological material that constitute other potential sources of DNA, for example: samples derived from neonatal screening, samples used for examinations of military personnel, the tissues preserved in pathological anatomy, and samples used in research laboratories, in pharmaceutical and/or biotechnological companies, in forensic medicine services, in transfusion

services, and in services for HLA typing. These collections are extremely numerous and varied; it is almost impossible to quantify them and to obtain information about their management and quality. Faced with the rising increase in genetic biobanks and the interests associated with them, we believe it imperative that in Italy there be a rapid regulation of their establishment and uses, and that a census be conducted of those already in existence. We offer this document as a starting point for a discussion towards formulating national guidelines and regulations for genetic biobanks, in line with most European countries [1-2] and the United States.

This document examines the definition of genetic biobanks, their purposes, management of sample data, the concept of confidentiality, the use and distribution of biological samples, and the benefits that can be achieved.

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1 Godard B., Schmidtke J., Cassiman J.J., Aymé S. "Data storage and DNA banking for biomedical research: informed consent, confidentiality, quality issue, ownership, return of benefits". A Professional Perspective. EUROGAPP PROJECT 1999-2000. ESHG 1 November 2002.

2 "Ethical aspects of human tissue banking". Opinion of the European Group on Ethics in Science and New Technologies to the European Commission. N. 11, 21 July 1998.

1 GENETIC BIOBANKS

1.1 DEFINITIONS AND CHARACTERISTICS

Biobanks are defined in international documents according to the different types of samples stored. According to the "Regulations" adopted for the *European Biobank* of the University of Maastricht, the term biobank is used to refer to "a service unit for reliable storage and automated management of biological material and corresponding data, complying with the Code of Good Use and the Code of Good Behaviour, and any additional guidelines of the Medical Ethics Committee and the University [3].

In a 1999 document, the Swedish Medical Research Council defines biobanks as collections of human tissue samples whose origin is always traceable, stored for a definite or indefinite period of time for specific research projects[4].

In Iceland the *DECODE* project has planned to collect DNA samples as well as personal and clinical data from the whole population, the biobank is "a collection of biological samples which are permanently preserved"[5].

European Council Recommendation R (94) 1 of March 14, 1994, defines a bank of human tissue as a non-profit organization that must be officially recognized by the competent health authority of the Member State, and must guarantee the treatment, preservation and distribution of the material[6].

By human tissue, we mean all parts of the body including surgical residues. The following are not considered human tissue: hair, nails, the placenta and body waste products.

Biobanks should not preserve biological material already regulated by specific legislations, such as: organs for transplants[7-8], blood and blood products for

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3 "REGULATIONS European Biobank Maastricht" Dr. F.F. Stelma, Dept. Epidemiology, Maasticht University, Jan. 2003

4 "Sweden sets ethical standards for use of genetics biobanks". A. Abott. Nature, vol. 400, p. 3, July 1999.

5 "Regulations on the keeping and utilization of biological samples in biobanks" No134/2001. Ministry of Health and Social Security – Reykjavik-Iceland.

6 "Recommendation N. R(94)1 of the Committee of Ministers to member states on human tissue banks". Council of Europe, 14 march 1994.

7 Commission of the European Communities: "Proposal for a Directive of the European Parliament and of the Council on setting standards of quality and safety for the donation, procurement, testing, processing, storage and distribution of human tissues and cells". Brussels, 19/6/2002.

8 Italian Law No.91 of April 1, 1999: "Disposizione in materia di prelievi e di trapianti di organi e tessuti".

transfusion purposes[9], embryos[10], sperm and oocytes for assisted reproduction.

We define **genetic biobanks as non-profit service units created for the collection and storage of human biological material used for genetic diagnosis, the study of biodiversity and for research. The specificity of genetic biobanks requires that the stored samples be linkable to the personal, genealogical and clinical data of the subjects from whom the deposited material has been collected.** Given that a real and proper genetic profile of the individual can emerge from the sum of these related data, it is imperative that regulations for the security and confidentiality of personal data be respected.

A characteristic of biobanks is the storage of biological material from which the DNA, namely *human genome,* can be extracted and evaluated on three levels: universal, familial, and individual.

UNESCO defines the *human genome* in a symbolic sense as the "heritage of humanity" and a "common human inheritance", and underlines the need to respect and protect the common characteristics of the human species, also for the benefit of future generations[11].

The *World Health Organization* (WHO)[12] and the *Human Genome Organization* (HUGO)[13] underline that genetic information is "familial" given that the genome is the patrimony of the family and connects the generations. Therefore, since the genome is not the property of the individual but is rather shared within the family (ascendants, descendants and collaterals), the right of biological family members to access the information and the samples themselves must be respected, provided that it be to the advantage of the health of the individual donor.

Finally, the "uniqueness" of an individual's genome is universally recognized[14]. Consequently, since it is possible to identify "a specific genome" among various DNA samples, it is necessary for biobanks to adopt very precise procedures to

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9 Italian Ministerial Decree No. 78 of January 25, 2001. "Caratteristiche e modalità per la donazione di sangue e emocomponenti".

10 "Identità e statuto dell'embrione". Italian Bioethics Committee, June 22, 1996.

11 "Universal Declaration on the Human Genome and Human Rights", Art. 1. UNESCO, International Bioethics Committee, Paris, 1997.

12 "Proposed International Guidelines on Ethical Issues in Medical Genetics and Genetic Services". World Health Organization, Geneva, 1998.

13 "International Ethics Committee Statement on DNA sampling: Control and Access". HUGO, London, 1998.

14 "Universal Declaration on the Human Genome and Human Rights". UNESCO, International Bioethics Committee, Paris, 1997.

guarantee the confidentiality of the data[15].

A special type of genetic biobanks are those that collect and store the biological samples of populations. These require a complex organization and adequate financing to manage an extremely high number of samples[16]. They are subject to the same regulations as discussed in this document, but particular emphasis must be placed on obtaining the informed consent of the community and on safeguarding the ethical principles regarding the donation of samples in the "contracts" that regulate the relationship with the public and/or private funders.

Genetic biobanks are characterized by the collection and storage of samples derived from:

- Individuals and families with genetic pathologies;
- Population groups with a high frequency of people who carry or are affected by genetic diseases;
- Populations with genetic characteristics ideal for the identification of susceptibility genes (i.e. populations with a reduced inter-individual variability, strong endogamy);
- Population groups that are ideal for the study of pharmacogenetics;
- Population groups used as controls.

1.2 GOALS

Genetic biobanks, the majority of which were created in response to the interests and research of single groups, attract the attention of the scientific community because they constitute a precious resource for the development of knowledge about the human genome.

The priority goals of genetic biobanks can be summarized as follows:

- To support research to identify the mutations that cause genetic diseases. These are usually rare or very rare; thus preservation of the samples from affected families and individuals in a single collection can lead to results that are useful for developing diagnostic tests, evaluating the reproduction risks of the carriers and for the application of possible treatments. This constitutes a significant advantage for individual families and their descendants who can

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15 Knoppers B.M. "Status, sale and patenting of human genetic material: an international survey". Nature Genetics 2, p. 23-26, 1999.

16 "Genebanks: a comparison of eight proposed international genetic databases". Community Genetics 6, p. 37-45, 2003.

hope to learn the cause of the family pathology in the near future.

- To study a collection of individuals with genomic characteristics that are useful for understanding the genetic basis of complex illnesses and the predisposition to diseases. These studies constitute the research challenge of the coming years; their success is conditioned by the availability of a large series of biological samples that are suited to different approaches (e.g. immortalised cell lines).
- To provide pharmacogenetic research with samples suitable for studying the genomic variations that are associated with different responses to pharmaceuticals. In fact, it has been known for years that an individual's predisposition to benefit from a drug or to have slight or severe side-effects can depend on genetic factors that are still not completely understood and which constitute the objective of the industry's research to produce more effective and personalized drugs.
- To centralize the collection of samples of specific genetic diseases in order to make available the cell lines that are indispensable for in vitro experimentation of innovative therapies, for example genetic therapies.
- To offer a service to researchers for the development of their studies and to facilitate communication and exchange of information among different groups of scientists.

2 BENEFITS TO THE COMMUNITY

Genetic biobanks, as explained above, constitute an important instrument for research. Positive results will bring benefits not only to the donor and his/her family, but also to the entire human community. This "advantage for the collective" is an important concept underlined in various documents; in particular, Article 12 of the "Declaration on the Human Genome"[17], states that "The applications of research, including applications in biology, genetics and medicine, concerning the human genome, shall seek to offer relief from suffering and improve the health of individuals and humankind as a whole". "Benefits from advances in biology, genetics and medicine, concerning the human genome, shall be made available to all, with due regard for the dignity and human rights of each individual". Not only should researchers work towards applying their results towards the common good, but, as Greely argues[18], whenever research uses samples of biological material it is generally assumed that the donor offers the sample for the benefit of the community rather than for personal profit or the exclusive profit of a private company[19].

There exists a fundamental ethic principle that "donated" biological material should not become a good of solely economic concern, but that the return of benefits to the community must be guaranteed. The European Group on Ethics in Science and in New Technologies has stated with respect to tissue banks: "all Member States of the European Union adhere to the principle that donations of human tissue must be free, following the example of blood, and this rules out any payment to the donor"[20].

The Ethics Committee of HUGO[21] recently published a statement on the shared benefits of genetic studies, recommending: 1) that all humanity share in, and have access to, the benefits of genetic research; 2) that the benefits not be limited to those individuals who participated in such research; 3) that there be prior discussion with groups or communities on the issue of benefit-sharing; 4) that even

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17 "Universal Declaration on the Human Genome and Human Rights". UNESCO, International Bioethics Committee, Paris, 1997.

18 Greely H.T. "The control of genetic research: involving the groups in between". Huston Law Review, 33, pg. 1397, 1997.

19 Godard B., Schmidtke J., Cassiman J.J., Aymé S. "Data storage and DNA banking for biomedical research: informed consent, confidentiality, quality issue, ownership, return of benefits". A Professional Perspective. EUROGAPP PROJECT 1999-2000. ESHG 1 November 2002.

20 Knoppers B.M. "Status, sale and patenting of human genetic material: an international survey". Nature Genetics 22, p. 23-26, 1999.

21 "Statement on benefit-sharing" HUGO Ethics Committee, 9 April 2000.

in the absence of profits, immediate health benefits as determined by community needs could be provided 5) that at a minimum, all research participants should receive information about general research outcomes and an indication of appreciation 6) that profit-making entities dedicate a percentage of their annual net profit to healthcare infrastructure and/or to humanitarian effort.

3 ETHICAL CONSIDERATIONS

Interest in the potential of genetic biobanks to benefit public health and research has increased sensitivity to the ethical implications. In the absence of specific legislation on these matters, human biological material and the related genetic data should be treated in a manner that guarantees the dignity, rights, and freedom of the individual in conformity with that established in a variety of documents, both national and international, on biomedical research and practices. Genetic biobanks must satisfy the following requirements for the handling of samples and data.

3.1 INFORMED CONSENT

The ethical justification for informed consent is established in Article 32, par.2 of the Italian Constitution[22]. More recently, the need for consent is also called for in Article 5 of the Oviedo Convention[23], Article 38 of the Code of Medical Deontology of the Italian Federation of Physicians[24] and Article 3 of the Charter of Fundamental Rights of the European Union (2000/C 364/01)[25].
The principal aspects of informed consent are:

- Information provided to the subject
- Mental, physical and legal capacity to express consent
- Freedom of choice

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[22] Constitution of the Italian Republic (1947), Art. 32: "La Repubblica tutela la salute come fondamentale diritto dell'individuo e interesse della collettività, e garantisce cure gratuite agli indigenti. Nessuno può essere obbligato a un determinato trattamento sanitario se non per disposizione di legge. La legge non può in nessun caso violare i limiti imposti dal rispetto della persona umana".

[23] "Convention on Human Rights and Biomedicine" Oviedo 4 April 1997. Art. 5: An intervention in the health field may only be carried out after the person concerned has given free and informed consent to it. This person shall beforehand be given appropriate information as to the purpose and nature of the intervention as well as on its consequences and risks. The person concerned may freely withdraw consent at any time.

[24] Italian Code of Medical deontology (1998), Art. 39: "Il prelievo di organi e tessuti da persona vivente è consentito solo se diretto a fini diagnostici, terapeutici o di ricerca scientifica se non produttivo di menomazioni permanenti dell'integrità fisica o psichica del donatore, fatte salve le previsioni normative in materia. Il prelievo non può essere effettuato per fini di commercio e di lucro e presuppone l'informazione e il consenso scritto del donatore o dei suoi legali rappresentanti".

[25] Charter of Fundamental Rights of the European Union (2000/C 364/01), Art 3.2.: "In the fields of medicine and biology, the following must be respected in particular: the free and informed consent of the person concerned, according to the procedures laid down by law; the prohibition of eugenic practices, in particular those aiming at the selection of persons; the prohibition of making the human body and its parts as such a source of financial gain; the prohibition of the reproductive cloning of human beings."

Personal Informed Consent

In the case of genetic biobanks, informed consent for the banking of a sample must be extended to its storage and possible use for diagnostic and/or research purposes. With respect to this aspect, even if not in explicit reference to biobanks, the European Convention of Oviedo establishes the legality of using stored samples only if adequate information is provided, anonymity is guaranteed and written consent is obtained[26].

The removal of a biological sample must be preceded by an interview in which the necessary information is provided, in a simple and comprehensible manner, so that the party concerned can take conscious decisions without any pressure or manipulation. Moreover, the person, if he or she so requests, should be allowed to consult third parties not involved in the research to clarify any doubts and obtain further information.

Informed consent for population studies

If a population becomes the subject of genetic research[27], it is believed that consent must be requested and obtained from each single person and not at the group level[28] [29]. The local authorities (civil, health, religious) and the bioethics committee that authorizes the project must become the guarantors of the correctness and transparency of the information regarding the scientific goals of the research, the progress of the programme, and the positive outcomes for the individual and the population. Furthermore, the right of any single individual to refuse to participate in the study should be protected without any form of pressure.

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[26] "Convention on Human Rights and Biomedicine" Oviedo 4 April 1997. Art.5: "An intervention in the health field may only be carried out after the person concerned has given free and informed consent to it. This person shall beforehand be given appropriate information as to the purpose and nature of the intervention as well as on its consequences and risks. The person concerned may freely withdraw consent at any time". Art. 22: "When in the course of an intervention any part of a human body is removed, it may be stored and used for a purpose other than that for which it was removed, only if this is done in conformity with appropriate information and consent procedures".

[27] "Genebanks: a comparison of eight proposed international genetic databases". Community Genetics 6, p. 37-45, 2003.

[28] Greely H.T. "Informed consent and other ethical issues in human populations genetics". Annual Reviews Genetics 35, 785-800, 2001.

[29] Godard B., Schmidtke J., Cassiman J.J., Aymé S. "Data storage and DNA banking for biomedical research: informed consent, confidentiality, quality issue, ownership, return of benefits". A Professional Perspective. EUROGAPP PROJECT 1999-2000. ESHG 1 November 2002.

3.1.1 PROCEDURES FOR SEEKING PATIENTS' CONSENT

Consent must be requested using a special form approved by the Ethics Committee of the body in which the genetic biobank is situated (Appendix 7.2). All aspects relative to the handling of the preserved material must be made explicit in the consent form.

Use of the sample: it should be clear that the sample may be used for further investigation of an exclusively diagnostic and/or research nature, and never for direct profit, in conformity with that established in Article 21 of the Oviedo Convention[30], Article 39 of the Code of Medical Deontology[31] and Article 3 of the Charter of Fundamental Rights of the European Union[32].

The type of information that might be derived from the use of the sample and the potential benefits for the health of the individual and/or the entire community should also be explained.

Confidentiality: the procedures for handling the data to ensure anonymity and the protection of confidentiality about the origin of the sample and the related investigations should be clarified (see Section 3.2).

Service guarantee: the responsibility for the handling and storage of the biological material rests with the institution where the genetic biobank is situated. All structural and management measures should be taken to preserve of the quality of the sample. That notwithstanding, it should be made clear that the institution cannot be held responsible for any possible accidental damage to the sample.

Withdrawal of consent: it should be made explicit that consent can be withdrawn at

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30 "Convention on Human Rights and Biomedicine" Oviedo 4 April 1997. Art 21: "Prohibition of financial gain: the human body and its parts shall not, as such, give rise to financial gain".

31 Italian Code of Medical Deontology (1998), Art. 39: "Il prelievo di organi e tessuti da persona vivente e' consentito solo se diretto a fini diagnostici, terapeutici o di ricerca scientifica e se non produttivo di menomazioni permanenti dell'integrità fisica o psichica del donatore, fatte salve le previsioni normative in materia. Il prelievo non può essere effettuato per fini di commercio e di lucro e presuppone l'informazione e il consenso scritto del donatore o dei suoi legali rappresentanti".

32 Charter of Fundamental Rights of the European Union (2000/C 364/01), Art 3.2: "In the fields of medicine and biology, the following must be respected in particular: the free and informed consent of the person concerned, according to the procedures laid down by law; the prohibition of eugenic practices, in particular those aiming at the selection of persons; the prohibition on making the human body and its parts as such a source of financial gain; the prohibition of the reproductive cloning of human beings."

any time; in this case, the sample and relevant information will be eliminated and no further data will be generated.

The subject who has received the information should have the possibility to take separate decisions regarding whether:

- *To authorize/not authorize* the preservation of his/her sample
- *To authorize/not authorize* the use of his/her sample for further studies or scientific research
- *To wish/not wish* to be informed about the results or diagnostic possibilities deriving from continuing research

After signing the consent form, the subject receives a copy countersigned by the person responsible for the Bank as a guarantee of the respect for the statements.

3.1.2 USE OF SAMPLES IN SPECIAL SITUATIONS

3.1.2.1 Samples in the absence of informed consent

The majority of biobanks storing genetic material have samples taken in the past from patients with rare genetic defects and stored without specific written informed consent. In 1996 the Executive Committee of the *American Society of Human Genetics* stated in a document that the use of this material is allowed only if the sample is rendered anonymous[33]. A document of the *European Society of Human Genetics* (2002) offers a different opinion: it is permitted to use these samples in an identifiable manner, even in the absence of informed consent, as long as the same protections are extended to the donor as are given to donors of samples with consent[34].

Following this latter view, we believe that the management of genetic biobanks should guarantee the confidentiality of the samples according to the rules of professional deontology and existing regulations, without the obligation to anonymise the samples, in order to be able to make any diagnosis available to biological family members and for research towards the common good. In this latter case, the bioethical committee of the structure that houses the bank should

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[33] American Society of Human Genetics, Statement on Informed Consent for Genetic Research, 1996. Am. J. Hum. Genet, 59: 471-4.

[34] Godard B., Schmidtke J., Cassiman J.J., Aymé S. "Data storage and DNA banking for biomedical research: informed consent, confidentiality, quality issue, ownership, return of benefits". A Professional Perspective. EUROGAPP PROJECT 1999-2000. ESHG 1 November 2002.

authorise the use of the biological material.

3.1.2.2 Samples taken from individuals unable to provide consent

Various documents address this issue. The Oviedo Convention and the Code of Medical Deontology both state that consent for the storage of samples taken from minors or adults with mental disorders must be provided by the legal guardian[35-36]. According to Article 2 of Legislative Decree No. 135 of July 29, 1999, consent can be provided by the person who exercises legal authority[37].

3.1.2.3 Samples for which informed consent is not possible

There are particular situations in which, for various and insurmountable reasons, it is impossible to obtain the informed consent of the donor of the biological material. These samples can be used for specific and limited purposes, if the potential benefits for the individual or the community are significant and all of the protections provided for samples with consent are guaranteed[38].

3.1.2.4 Samples obtained from abortions

Italy does not have a specific law on the preservation of fetal cells, tissues and organs, but we can, following other documents and regulations, propose some general rules.

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35 Italian Code of Medical Deontology (1998), Art. 33: "Allorché si tratti di minore, interdetto o inabilitato il consenso agli interventi diagnostici e terapeutici, nonché al trattamento dei dati sensibili, deve essere espresso dal rappresentante legale".

36 "Convention on Human Rights and Biomedicine" Oviedo 4 April 1997. Art. 6: "Protection of persons not able to consent; par. 2) where, according to law, a minor does not have the capacity to consent to an intervention, the intervention may only be carried out with the authorisation of his or her representative or an authority or a person or body provided for by law. The opinion of the minor shall be taken into consideration as an increasingly determining factor in proportion to his or her age and degree of maturity.; par. 3) where, according to law, an adult does not have the capacity to consent to an intervention because of a mental disability, a disease or for similar reasons, the intervention may only be carried out with the authorisation of his or her representative or an authority or a person or body provided for by law".

37 Italian Legislative Decree of July 29, 1999, "Disposizioni in materia di trattamento dei dati personali in ambito sanitario". Art. 2. "Informativa e consenso 1-quater. In caso di incapacità di agire, ovvero di impossibilità fisica o di incapacità di intendere o di volere, il consenso al trattamento dei dati idonei a rivelare lo stato di salute è validamente manifestato nei confronti di esercenti le professioni sanitarie e di organismi sanitari, rispettivamente, da chi esercita legalmente la potestà ovvero da un familiare, da un prossimo congiunto, da un convivente, o, in loro assenza, dal responsabile della struttura presso cui dimori".

38 Godard B., Schmidtke J., Cassiman J.J., Aymé S. "Data storage and DNA banking for biomedical research: informed consent, confidentiality, quality issue, ownership, return of benefits". A Professional Perspective. EUROGAPP PROJECT 1999-2000. ESHG 1 November 2002.

Above all, it is important to distinguish between spontaneous abortions and induced abortions, and among these latter, those which followed the identification of fetuses with genetic pathologies and/or malformations[39]. Putting aside, then, abortions done for social reasons (IVG, Law 194, 1978), for the others the storage of biological samples must follow the procedures recommended by the National Bioethics Committee whenever an investigation is requested to identify the cause of the interruption of the pregnancy or of the fetal pathology, or whenever these samples are used for research or experiments: "the following are considered morally permissible: experiments on dead embryos obtained from spontaneous or induced abortions as long as the parents give their free and informed consent and the independence between the medical personnel and/or institution that practiced the voluntary abortion and those who will conduct the experiment is established"[40]. According to the spirit of Law 194/78, the mother's consent can be sufficient.

The consent of the mother can be omitted if the aborted material derives from the interruption of a pregnancy for social reasons within the first twelve weeks and the samples remain anonymous. If for any research motive it is necessary to trace the biological material to its origin, consent must be requested.

Finally, it is emphasized that, as for any experimental research on humans or any part of human beings, projects that include the use of aborted material must receive the binding approval of the bioethics committee of the relevant institution.

3.1.2.5 Samples coming from abroad

In cases involving samples from abroad, the manager of the genetic biobank should request a copy of the consent form signed by the donor and/or the requesting physician in order to ascertain that the sample was obtained in a manner that respects the privacy of the donor and in conformity with the existing regulations in the country of origin.

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[39] Italian Law No. 194 of May 25, 1978, Art. 4, 5, 6, 7 : "Norme per la tutela sociale della maternità e sull'interruzione volontaria della gravidanza".

[40] "Identità e stato dell'embrione". Art. 8.2.2 Italian Bioethics Committee, June 22, 1996.

3.2 PROTECTION AND TREATMENT OF CONFIDENTIALITY

The protection of confidentiality is one of the most important issues in the management of a genetic biobank.

Various European documents address the problem, in particular European Directive No. 95/46/CE on the protection of individuals with regard to the processing of personal data[41]. In Italy, the issue is regulated by Legislative Decree n. 196 of June 30, 2003.[42] What emerges from the principles expressed in these documents is the need to implement certain procedures with respect to the access and the communication of the data, the possible involvement of family members and the measures adopted for protecting confidentiality.

The protection of personal data by the biobank avoids the risk of any form of discrimination based on genetic characteristics, on the part of employers or insurance companies, in conformity with Article 21 of the Charter of Fundamental Rights of the European Union[43] and Article 11 of the Oviedo Convention[44].

3.2.1 REGISTRATION OF THE SAMPLE

In general, the labelling of a sample can range from irreversible anonymity to complete identification, following the different conventional methods used for classifying samples[45-46].

- Anonymous: samples collected and immediately identified only by a code. The patient's data are not recorded; it is therefore impossible to trace back

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41 Directive 95/46/CE of the European Parliament and of the Council of 24 October 1995 on the protection of individuals with regard to the processing of personal data and on the free movement of such data.

42 Italian Legislative Decree of June 30, 2003, No. 196 "Codice in materia di protezione dei dati personali".

43 Charter of Fundamental Rights of the European Union (2000/C 364/01), Art. 21.1: "Non-discrimination: Any discrimination based on any ground such as sex, race, colour, ethnic or social origin, genetic features, language, religion or belief, political or any other opinion, membership of a national minority, property, birth, disability, age or sexual orientation shall be prohibited."

44 "Convention on Human Rights and Biomedicine" Oviedo 4 April 1997. Art. 11: "Non-discrimination: any form of discrimination against a person on grounds of his or her genetic heritage is prohibited".

45 "Data storage and DNA banking for biomedical research: informed consent, confidentiality, quality issue, ownership, return of benefits". EUROGAPP PROJECT 1 November 2002.

46 Emea/CPMP "Position paper on terminology in pharmacogenetics" 21 November 2002.

to the source.

- Anonymised: the patient's personal data are removed after a code is assigned, after which it is no longer possible to connect the two.
- Identifiable: samples identifiable through a code known only to the person in charge of the biobank and his/her immediate colleagues. The possibility of tracing the sample back to its donor is acted upon only in the event of scientific results of use to the donor, on the basis of the choices expressed in the written informed consent form. Tracing samples back to their donors is not necessary when samples are used for scientific purposes only, since this information is neither useful nor necessary to the donor.
- Complete identification: the sample is identifiable by name and address. This option is only possible upon explicit request by the interested party and in any case only for the exclusive personal and family use (for example for diagnosis).

As mentioned above, genetic biobanks can be useful not only for current generations but also for future ones given the status (family patrimony) of the stored material. As a result, it is essential that the possibility of identifying each stored sample be maintained.

The procedure for coding samples is paramount to the protection of the donor's privacy as well as for allowing distribution and use for research purposes. The registration of the sample must follow existing regulations[47-48-49] and respect all the choices expressed by the party concerned in the written consent form.

The personal details of the subject or other information that can lead easily to the source of the sample should never appear on the label, clinical chart or other material unless expressly aimed at the maintenance of the data.

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47 Italian Law n. 675, December 31, 1996: " Tutela delle persone e di altri soggetti rispetto al trattamento dei dati personali" Art. 23 par. 1) Gli esercenti le professioni sanitarie e gli organismi sanitari pubblici possono, anche senza l'autorizzazione del Garante, trattare i dati personali idonei a rivelare lo stato di salute, limitatamente ai dati e alle operazioni indispensabili per il perseguimento di finalità di tutela dell'incolumità' fisica e della salute dell'interessato. Se le medesime finalità riguardano un terzo o la collettività, in mancanza del consenso dell'interessato, il trattamento può avvenire previa autorizzazione del Garante; par. 4). La diffusione dei dati idonei a rivelare lo stato di salute è vietata, salvo nel caso in cui sia necessaria per finalità di prevenzione, accertamento o repressione dei reati, con l'osservanza delle norme che regolano la materia".

48 Italian Legislative Decree of July 29, 1999, "Disposizioni in materia di trattamento dei dati personali in ambito sanitario".

49 Italian Administrative Measure September 20, 2000. "Garante per la protezione dei dati personali. Autorizzazione al trattamento dei dati idonei a rivelare lo stato di salute e la vita sessuale. (Provvedimento n. 2/2000)".

3.2.2 DATA MANAGEMENT

The data files can be kept either on paper or electronically, with either method subject to an encoding procedure. In order to guarantee anonymity, the biobank should use two different databases; one for the data relative to the biological material, accessible from the outside, for example through an internet site to allow the circulation of the samples, and one for storing the personal data of the donor, never available to outsiders. Access to the databases should be restricted to the personnel of the bank and protected by security systems.

Even in the paper file, the code that links the donor and his/her data is registered and stored separately. The paper file includes:

1. a file with the donor's name, the date of arrival and the assigned code;
2. a file that lists the various samples only by code and all the relevant information (type of material, the possible diagnosis and the centre of origin, technical data and any notes on their uses, including the order form).
3. the documents relative to each sample (the subject's clinical chart, the consent form, the deposit form, etc.).

All paper documentation should be kept under lock and key in two separate filing cabinets: one containing documents in points 1 and 3 and the other containing those in point 2.

Access to the information is restricted to the person in charge in the biobank and a delegate.

3.3 IMPLICATIONS FOR OWNERSHIP AND USE OF HUMAN BIOLOGICAL MATERIAL

The person who agrees to the use of his/her biological material deposited in a genetic biobank offers a gift of incalculable value to the community that fosters research towards both an understanding of the pathology and the development of new diagnostic and/or therapeutic approaches. Nonetheless, the commercial implications associated with these results and the potential profits that can follow make it necessary to define in a clear manner the ethical-legal position of the biobank that handles the samples.

The issue of the "commercialisation" of biological material is still the subject of broad debates and deliberations and is closely related to the concepts of "ownership of tissues", "patentability of living material", and "freedom of scientific

research".

The principal issue relates to the definition of the legal status of the human body and the ownership of the tissues it possesses. The most recent and authoritative points of reference are the following. The UNESCO Declaration (1997) states that the human genome is the patrimony of humanity and the family[50]. The Oviedo Bioethical Convention (1997) protecting human dignity, establishes that the body and its parts, as such, cannot be the source of financial gain; nonetheless, the document clarifies that the drawn material can be stored or used for a variety of purposes as long as there exists the informed consent of the donor[51]. Finally, the Directive of the European Parliament and the Council on the legal protection of biotechnological inventions (98/44/CE) specifies the limits on the patentability of biological material[52].

Therefore, the general tendency is to protect the human body and its genome from any form of economic exploitation while recognizing the possibility of financial gain related to the intellectual property that derives from the inventive work. Given the importance of the issue and the related ethical and social implications, some European countries, including Italy, have not yet adopted Directive 98/44/CE.

It is therefore necessary for the legislator at the community level to define in a clearer fashion the issue of ownership of genetic information and patents, on the basis of the fundamental principles of equity and liberty that must be at the foundation of the development of biomedical technologies.

In the absence of a specific regulation, it must be made clear to the donor that his or her material stored in a genetic biobank will never be exploited for direct

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50 Universal Declaration on the Human Genome and Human Rights, UNESCO (1997). Art 1: "The human genome underlies the fundamental unity of all members of the human family, as well as the recognition of their inherent dignity and diversity."

51 "Convention on Human Rights and Biomedicine" Oviedo 4 April 1997. Art. 21: " "Prohibition of financial gain: the human body and its parts shall not, as such, give rise to financial gain".

52 Directive 98/44/CE of the European Parliament and the Council of 6 July 1998 on the legal protection of biotechnological inventions: Art. 3: "inventions which are new, which involve an inventive step and which are susceptible of industrial application shall be patentable even if they concern a product consisting of or containing biological material or a process by means of which biological material is produced, processed or used. Biological material which is isolated from its natural environment or produced by means of a technical process may be the subject of an invention even if it previously occurred in nature". Art. 5.1 "The human body, at the various stages of its formation and development, and the simple discovery of one of its elements, including the sequence or partial sequence of a gene, cannot constitute patentable inventions." Art.5.2: "An element isolated from the human body or otherwise produced by means of a technical process, including the sequence or partial sequence of a gene, may constitute a patentable invention, even if the structure of that element is identical to that of a natural element".

profit, but could give rise indirectly to financial gain in connection with, for example, the development of therapies or diagnostic tests. In this case, it should be clear that neither the donor nor the researcher will derive any personal financial gain, but that the genetic biobank will protect the interests of the community to which the subject belongs, so that any profits might be invested in future research and works and services of use to the collective.

4 ORGANIZATION

The establishment of a genetic biobank must be authorised by the institution where it is situated in so far as this latter must share the responsibility for its operations (e.g. structure, personnel, funding). We nevertheless believe that it is essential that genetic biobanks be inserted in regional programming and be certified by specific regulations.

Genetic biobanks must be organized in a manner that ensures:

1. the privacy of the donor;
2. the quality of the sample;
3. the storage of the sample for the longest possible time;
4. the correct use and distribution of the sample.

To guarantee these services, genetic biobanks should follow specific procedures governing both technical aspects – registration, handling and storage of the sample, quality control – and the filing of clinical, personal and genealogical data.

When a genetic biobank is no longer able to function due to serious problems, the samples should be protected and transferred to other biobanks.

4.1 STRUCTURAL AND TECHNOLOGICAL REQUIREMENTS

Genetic biobanks should be placed within specialized laboratories, for example the Laboratories of Medical Genetics , with appropriate and specific premises, and should follow the regulations utilized by the National Health System, the University and affiliated private institutions regarding personnel, equipment and organization.

In particular, the laboratory of a genetic biobank should be established according to the security regulations governing the use of viruses in culture applied to cell immortalisation (for example EBV) and cryofreezing in liquid nitrogen[53]. It must further possess its own equipment: CO2 incubators; sterile laminar hood flow for cell cultures (biohazard); freezers; equipment for cryopreservation; inverted microscope; centrifuge; computer systems for the management of data and internet connection. Archived data must be protected from intrusions and

[53] Italian Legislative Decree 626/94, "Miglioramento della sicurezza e della salute dei lavoratori sul luogo di lavoro". Art. 75,82 e allegato XI.

interruptions of the system (see Sections 3.2.2 e 6.4).

It is desirable that specific and uniform (at the national and European levels) certification procedures be developed for genetic biobanks.

4.2 PERSONNEL

The permanent staff of the laboratory where the biobank is situated must include the following:

- A doctor or biologist in charge (with the valid legal requisites as established for structures of the National Health System and affiliated structures);
- health personnel dedicated exclusively to the activities of the biobank
- administrative personnel for the handling of the data.

The number of people who work in a biobank varies according to the volume of activity, whose continuity must nonetheless be guaranteed.

5 TYPOLOGY OF STORED SAMPLES

Genetic biobanks store the following types of human biological samples:

- human tissue samples;
- human cell lines;
- DNA samples;
- transgenic/engineered material.

In this context, collections of biological material derived from neonatal screening, such as the "Gutrie cards", archives of paraffinated tissues in pathological anatomy laboratories, and DNA samples from forensic medicine cannot be defined as genetic biobanks. Indeed, the use and regulation of these collections are different from those for genetic biobanks in so far as the material is used and stored for specific purposes (diagnosis, screening, forensic medicine) and not according to the criteria that characterise genetic biobanks.

These archives represent, however, an extremely precious and potentially useful patrimony for diagnostic and research purposes, with the same modalities as that preserved in genetic biobanks. It is emphasised that collections of fixed and even paraffinated tissues must necessarily be sampled and classified by a hospital department of pathological anatomy.

6 SERVICES

6.1 ACCESS TO SERVICE

Access to the service must be preceded by contact with the person responsible for the Bank, who provides the following necessary information:

- Request form (appendix 7.1)
- Informed consent form (appendix 7.2)
- Chart for patient's clinical and personal data (6.1.1.)

6.1.1 CHART FOR PATIENT'S DATA

The patient's data, collected by the referring physician in a pre-printed chart, must include the following information:

- personal data (name, date of birth, address, ethnic origin)
- sex
- phenotype (affected/not affected)
- essential anamnestic data
- tests performed
- presence of consanguinity
- presence of familiarity
- pedigree
- clinical information (tissue and/or organ anomalies, laboratory anomalies)

In the presence of diagnosis

- Specification of the disease and the corresponding OMIM
- Modality of the diagnosis (clinic, laboratory)
- Centre performing diagnosis

In the absence of diagnosis

- An indication of the suspected diagnosis

6.1.2 ACQUISITION OF SAMPLES

In acquiring a sample, the personnel in charge of the biobank have the obligation to verify:

- Suitability of the packaging
- Quality of the sample
- Accuracy of labelling
- Presence of adequate forms (request form, informed consent form properly filled in, data chart)

6.2 BIOLOGICAL MATERIAL BANKING

The Bank agrees to store biological material already prepared in other centres, on the condition that it is compatible with its regulations and guidelines.

To request this service, the researcher who plans to deposit material must fill out a pre-printed form (Appendix 7.1) that provides the following information:

- Name, affiliation, address, telephone and fax numbers, and email address
- Type of biological material for the storage
- Availability/restrictions on use of sample for research purposes.

In signing the request form, the user agrees that they understand and accept the guidelines of the genetic biobank, which include the following points:

- The material must be collected in compliance with the privacy law
- In the event of publication of results obtained on material stored in the biobank, the authors promise to cite the origin of the sample, to acknowledge the biobank for the service provided, and to send a copy of the publication to the biobank.

In accordance with the biobanks guidelines, the mailing of the sample must be accompanied by a written consent form, the chart with the patient's data filled in by the referring physician, and the information relative to the biological material (in the case of cell lines: medium used, number of passages, possible problems with growth, contamination, etc.) .

6.3 DISTRIBUTION

The distribution of samples stored in a genetic biobank should take place only for "valid reasons", must be free (except to cover any direct costs of the material and the mailing) and should be reserved to donors and researchers working in qualified structures who explicitly state the purpose for using the samples.

In requesting the sample, the principal investigator must fill out a form (Appendix

7.4) that provides the following information:

- name, address, affiliation, telephone and fax numbers, and email address;
- type of sample requested;
- intended use of, briefly describing the research project and its goals.

In signing in the request form, the user acknowledges that they understand and accept the guidelines of the genetic biobank, which include the following points:

- the material cannot be used for commercial purposes;
- the material cannot be distributed to other researchers without written consent from the person responsible for the biobank;
- in the case of publication of results obtained using material stored in the biobank, the authors must state the origin of the samples, to acknowledge the biobank for the service provided, and to send a copy of the publication.
- No sample will be sent without the signed request form.

If upon evaluation by the person responsible for of the biobank, the request is considered suitable and in line with the guidelines of the Bank, the following steps will be taken:

- Recovery of the sample;
- execution of standard quality controls;
- mailing of sample in anonymity, accompanied by a two-part informational chart. The first part concerns the patient and provides a brief clinical and informational synthesis: age, diagnosis, OMIM, modality and centre responsible for the diagnosis; the second contains the characteristics of the sample and the details about the procedures adopted for its storage (Appendix 0).

In distributing a sample, the biobank assumes the responsibility for the identity of the samples and their quality (in the case of cell lines, the vitality of the cells and the absence of contamination by mycoplasma, bacteria, fungus; in the case of nucleic acids, the integrity of the sample).

Nonetheless, the genetic biobank is not responsible for the diagnosis linked to the sample.

The genetic biobank promises to attach to the sample the informational chart with the diagnostic indications provided by the structure that deposited the biological material.

6.4 PROCEDURES FOR ENSURING THE QUALITY OF THE SAMPLES

Strict quality control procedures are necessary for all procedures performed within the biobank.

Any equipment must be subject to periodic maintenance checks
Procedures governing the sterilisation of reagents and laboratory materials must be guaranteed.

The laboratory should develop standard procedures for quality control of the samples, written up in a manual at the disposal of the personnel.

Laboratories of cell cultures must implement methods that ensure cell lines that are not contaminated by mycoplasma, bacteria and fungus during the expansion, storage and after the thawing of the liquid nitrogen.

The integrity of nucleic acids should be evaluated using electrophoretic analysis on agarose gel. Their proper storage requires that a variety of aliquots be preserved for each sample, preferably in separate freezers. The freezers should be equipped with an alarm system that ensures an immediate intervention in case of an electrical blackout and the safeguarding of the samples. If an alarm system is unavailable, other measures must be taken to guarantee the correct preservation of the samples in case of an electrical blackout.

A similar procedure should be adopted for biological material stored in liquid nitrogen. The cryotubes containing samples from the same line should be separated into two different containers. Access to the storage room should be controlled and limited exclusively to personnel adequately trained to handle liquid nitrogen. The level of liquid nitrogen should be checked regularly and periodically replenished when necessary.

An identification number and corresponding location should be recorded for each stored sample. For cell cultures, the number of passages and any problems with growth and/or contamination should also be recorded.

7 APPENDICES

7.1 SUBMISSION FORM

Please, fill in all applicable items, sign the form, then send to:

Dr. ……

Address _____

Fax _____ **e-mail** _____

SUBMITTING INVESTIGATOR _____

Institute _____

Address _____

Phone _____ **Fax** _____

e-mail _____

TYPE OF SERVICE

ESTABLISHMENT OF CELL LINES ☐ DNA/RNA **EXTRACTION** ☐ **ANALYSIS** ☐

>>> Please, specify type of test requested _____

BANKING **YES** ☐ * **NO** ☐

SAMPLE INFORMATION

TYPE OF SAMPLE SUBMITTED Date _____

TISSUE: Peripheral blood ☐ Skin biopsy ☐ Amniotic fluid ☐ Other _____

CULTURE: Fibroblast ☐ Amniocyte ☐ Chorionic villus ☐

Lymphoblast ☐ Other _____

FOR CELL LINES, SPECIFY Date originally established: _____

Passage of submitted culture _____ Medium, serum (type and %) _____

Other useful details for growth and freezing _____

IN CASE OF BANKING,

please, specify availability of deposited samples for use by third parties for research purposes **YES** ☐ **NO** ☐

By signing this form the Investigator agrees to the following conditions:

- To provide clinical and laboratory documentation of the donor subject
- To send appropriate written informed consent obtained from the donor subject
- Not to use the banked sample for commercial purposes
- To quote the Biobank in the acknowledgements of any scientific production, specifying the origin of the sample, and to send a copy of the published work to the Biobank.

Place, Date **Signature of Investigator**

7.2 EXAMPLE OF INFORMED CONSENT FORM

The undersigned…… born in……..on……./…./……

Residing at……..Prov……..CAP……..

……n°……Tel……

after being informed that:

- The sample may be stored at the Biobank "……"
- The sample may be used for further investigations of an exclusively diagnostic and/or research nature, and never for direct profit
- Anonymity and confidentiality will be guaranteed with respect to the origin of the sample and the relative investigations
- All appropriate procedures will be taken to guarantee the suitability of the sample; however, the biobank does not assume responsibility for any damage or accidents that might occur.
- A change of opinion with respect to that declared can be communicated at all times; in this case, the sample and linked data will be eliminated and will not be used in future research

DECLARES TO:

1) ☐ authorise ☐ not authorise

the storage in the forenamed Bank of the biological material belonging to:

☐ self ☐ name…… relationship to authorising party……..

2) ☐ authorise ☐ not authorise

the possible use of said biological material for scientific studies or research

3) ☐ request ☐ do not request

to be informed of possible results concerning health that derive from said studies or research.

Date…… Signature……..

Health personnel who has collected the consent:

Surname and name……..

Office/Institute……..

Tel./Fax……..

The undersigned…… responsible for the Bank, guarantees respect for the above declarations.

Date Signature of person in charge of Biobank

7.3 ORDER FORM

Fill in, sign and send via mail or fax to:

Bank			
Address			
Fax		**e-mail**	

Researcher			
Project title			
Principal Investigator			
Financed by		**Proj. n°**	
Institution			
Address			
Telephone		**Fax**	
e-mail			
Characteristics of the requested sample(affected, non affected, type of disease….)			

Specify ☐ **DNA** ☐ **Cell line** ☐ **Tissue**

Description of project (briefly describe the project and results expected from the use of the sample)	

I, the undersigned, accept the following conditions:

- The material cannot be used for commercial purposes
- The material cannot be distributed to others without the written consent of the Biobank

I further commit to

- Pay the mailing costs
- Quote the Biobank in the acknowledgements of any scientific production, specifying the origin of the sample, and to send a copy of the published work to the Biobank.

Place, date **Signature of researcher**

7.4 SECURITY MEASURES FOR CELL LINES

Biological risk

In the handling cell lines of human or animal origin, even in the absence of infectious viruses or toxic products, it is advisable to follow the norms concerning the use of biological agents [54].

Information on the security of the sent material

- Frozen vials

The cryotubes contain cells in frozen medium containing dimethyl sulfoxide (DMSO) or glycerol (10% v/v)[55]. The package contains dry ice that can cause burns on contact with skin. It is possible, although highly improbable, that traces of liquid nitrogen remain in the vials. When heated, these vials pose the risk of explosion.

- Cells in culture

The cultures are mailed in 25-cm^2 flasks filled with culture medium supplemented with fetal bovine serum and HEPES buffer. The flasks, sealed with film and protected with absorbent and unbreakable material, are mailed in an appropriate container.

Procedures for handling frozen vials upon receipt

- Storage of cells

If the vial is not used immediately, it should be stored in gas-phase liquid nitrogen.

- Thawing the cells

1. Extract the vial from the container of liquid nitrogen with care, wearing gloves and a protective mask.
2. Perform rapid thawing by transferring the vial to water heated to 37°C per 30''-1' (the vial should never be completely immersed in the water) and swirling it.
3. Wipe the vial with a tissue saturated with disinfectant before opening it.
4. Add 0.5 ml of medium pre-heated to 37°C, and transfer the content to a sterile test-tube containing 10 ml of medium and centrifuge for 5 minutes at 150 - 200xg.
5. Resuspend the cells in 7-8 ml of appropriate culture medium and plate the cells in a 25cm^2 flask and place in the incubator.

Procedures for handling cells in culture upon receipt

Check the cells' viability through an inverted microscope and place them in an incubator at 37°C, CO_2 5%.

- Adherent cells

1. Eliminate most of the medium, leaving only enough to cover the cells (5-8 ml per

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[54] Italian Legislative Decree No. 626/94 - Articles 75, 76, 77 and Decree of the Ministry of Labour and Social Security, November 12, 1999. Norm concerning the use of biological agents.

[55] Security measures for laboratory chemical products. (http://www.zetalab.it/schede/schedeD.html).

25-cm^2 flask) and place in an incubator.
2. When confluent, eliminate the culture medium, wash twice with sterile PBS and detach the cells with 0,5 ml of trypsin-EDTA.
3. Incubate at 37°C until the cells detach, usually for 3-5 minutes unless otherwise indicated.
4. Resuspend the cells in fresh culture medium and plate the cells at the recommended density.

- Cells in suspension

1. Place the cells in a test-tube and centrifuge at 150-200xg for 5 minutes.
2. Resuspend the cells in fresh medium at the recommended density.

Note: some cell lines, and in particular those that tend to form aggregates, should not be centrifuged but rather diluted in fresh medium.

Procedures for disposal

The liquid waste materials should be deactivated with sodium hypochlorite for one night and placed in an appropriate container.

Solid waste material (cryotubes, flasks, pipettes) should be collected in an appropriate container (biobox) and disposed of in conformity with security norms.

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