RECOMMENDATIONS ON THE ETHICAL ASPECTS OF COLLECTIONS OF SAMPLES OR HUMAN TISSUE BANKS FOR BIOMEDICAL RESEARCH PURPOSES

Ethics Committee of the Rare Disease Research Institute

(Comité de Ética del Instituto de Investigación de Enfermedades Raras - CEIIER)

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TABLE OF CONTENTS

I. INTRODUCTION

II. BIOBANK FEATURES

III. RECOMMENDATIONS

   Biobank organisation and operation
   Recommendation 1. Institutional support of biobank
   Recommendation 2. Access to information and samples
   Recommendation 3. Advisory Ethics Committee
   Recommendation 4. Advisory Scientific Committee

   Degree of identification of samples
   Recommendation 5. Definition of degrees of identification of samples

   Safeguards for biobank data-management
   Recommendation 6. Information and data-protection system

   Consent to participate in research and have samples incorporated into a biobank
   Recommendation 7. Incorporation with informed consent
   Recommendation 8. Informed consent for subsequent studies
   Recommendation 9. Procedure for obtaining informed consent
   Recommendation 10. Informed consent in the case of minors or subjects lacking capacity to consent
   Recommendation 11. Ethics Committee approval of the consent form and explanatory note
   Recommendation 12. Right to withhold and revoke consent
   Recommendation 13. Informed consent for storage of samples left over from healthcare procedures

   Right to know and right not to know
   Recommendation 14. Information furnished to source subjects

   Consent for release of samples to third parties
Recommendation 15. Conditions for release and supervision by the Ethics Committee

Taking of post-mortem samples
Recommendation 16. Consent and objections

Management of historical collections of biological samples
Recommendation 17. Conditions for the retrospective use of samples

Ownership and marketing of samples and research results
Recommendation 18. Altruistic surrender

Return of benefits to the community
Recommendation 19. Shared enjoyment of benefits
I. INTRODUCTION

Filed away in hospital pathology departments are samples that have been taken from surgical procedures and stored for over a century, without this ever giving rise to dilemmas of an ethical or social nature. With the advent of new technologies that, on the one hand, enable all manner of samples to be stored, including cells that can remain alive indefinitely outside the human body, and on the other hand, enable scientific information of all types, including genetic information, to be obtained from these, a universe of possibilities for research in biomedicine has been opened up. All this has led to the emergence of complex ethical questions, not always free of controversy, and the need to address the justification for historical collections and the establishment of new collections -or human tissue banks- from a bioethical perspective.

Nowadays, collection of human biological matter and related information, as well as storage practices and use of samples in biomedical research, call for special consideration, inasmuch as there are important ethical aspects that concern both the individuals from whom the samples are taken, and the health professionals responsible for handling such samples, researchers and society in general.

Bar the occasional exception, current collections and databases suffer from a lack of definition, and most of the institutions that house them have no written guidelines or agreements governing such activity. The rules for sharing and exchanging information and biological matter are not clear, and awareness of the problems linked to the return of benefits to the research subjects or the community in general, is rather recent. Moreover, it is difficult to separate public from private research, e.g., public- and private-sector researchers might be working along the same lines, thereby giving rise to potential conflicts of interest.

The interests of researchers and society are not necessarily at odds, and development of protocols, good practice guidelines and ethical recommendations will favour society’s recognition of and trust in the honesty of research and its altruistic goals.

In the collection and storage of human biological material for research purposes, the principle of autonomy must be preserved, with this being construed as the right enjoyed by
every individual to accept or refuse his/her collaboration in research and the principle that no-one should be forced to contribute to such research. Similarly, guarantees are to be given to ensure that participants' rights and well-being in research are protected, and that these are to prevail over the interests of society and science. This implies protection, not only against physical risks, but also against psychological and social risks, and even any moral harm that might flow from the misuse or mismanagement of the ensuing information (e.g., discriminatory treatment or stigmatisation, communication of the information to third parties, or use that clashes with the values held by participants), with minors and vulnerable subjects deserving special consideration.

Based on a critical review of the most relevant points, this document therefore seeks to draw up some recommendations in the hope that these may serve to guide and foster responsible debate and discussion among all parties involved.

Ethical aspects are inevitably closely linked to legal aspects. Yet, in this document the intention is to lay greater emphasis on the ethical problems that might arise from the collection and use of samples for research purposes. Furthermore, a review of the legislation governing these matters in neighbouring countries was recently published,¹ so that legal aspects will not form a specific topic area of this document. Likewise excluded from these recommendations are ethical problems arising from the use of embryo and foetal tissue, human cells or tissue and by-products, intended for application to human beings, since these are covered by specific guidelines and have their own particular ethical connotations. Similarly, use of samples for forensic purposes is also excluded.

II.- BIOBANK FEATURES

Whereas the activity of collecting human matter for clinical and public health purposes is an historical fact in medicine, the concept of a biobank is a very recent development, is

applied to collections of samples of widely differing types, magnitudes and purposes (albeit mainly DNA), and, moreover, entails the creation of a related database.\(^2\)\(^,\)\(^3\)

Biobank origins and applications are multifold and include: banks prospectively established for a specific research project; banks of samples that are collected as part of health interventions (e.g., collections of samples remaining after neonatal screening programs) and are available for use in future biomedical research; banks set up for forensic and criminal research purposes; and banks established essentially for identification purposes (such as those set up by the armed forces in certain countries). Population banks have also been set up by government decision, with general interest goals such as searching for prevalences of specific genes and their variants in populations, simplifying the search for disease-predisposition biomarkers, examining interactions between environmental genes and factors, improving the discovery of treatment targets, refining disease-prevention strategies, or furnishing the necessary data for evidence-based decision-making vis-à-vis individuals, families and populations.

Some of the uses of bio banks were inconceivable just a few years ago, and technological advances have followed upon one another with such speed that it is difficult to forecast all their future research potential.

Tissue or cells (haematic cells, fibroblasts, osteoblasts, etc.) contain DNA and are thus a direct source of information and genetic research. These plus other matter, such as body fluids, serum and urine, are likewise useful for obtaining information on genetic characteristics, for research into genomics, proteomics, metabonomics, cytomics, etc., and also constitute valuable reference material for development of diagnostic and healthcare applications in general.

A good part of the scientific interest in such samples currently centres on genetic information, and a considerable proportion of biobank bibliography refers to banks of DNA already extracted from some biological material.


\(^3\) Biomedical Research Bill (Proyecto de Ley de Investigación Biomédica) 121/104, Parliament Gazette (Boletín de las Cortes), No. 104 of 22 September 2006.
There is a perception on the part of society that genetic information corresponds to personal information of a more sensitive type, in that, on the one hand, it may contain characteristics that identify the source subject,\(^4\) and on the other, it contains data pertaining to the family (and, sometimes, even the community or population) setting, thereby conceivably giving rise to a sense of apprehensiveness with regard to any possible misuse. As a result, it is claimed that such genetic information calls for exceptional legal treatment and protection measures, a stance that has been dubbed “genetic exceptionalism”. Yet, genetic information forms part of the complete spectrum of health information and does not per se constitute a separate category, i.e., all medical, including genetic, data require quality levels and confidentiality safeguards of the same calibre as those recently indicated by the European Commission.\(^5\)

From the viewpoint of the relevant ethical principles in biomedicine (justice, non-maleficence, autonomy and beneficence), there are no arguments that would justify a range of differentiated treatment as between DNA banks or the matter they contain and other types of human material biobanks (even though these may not contain DNA) having healthcare, research or public health purposes. The ideas and recommendations contained in this document are, thus, equally applicable to all.

III. RECOMMENDATIONS

Biobank organisation and operation

*Recommendation 1. A biobank must have institutional support. The institution that houses the biobank is responsible for its custody and should provide it with a structure, an organisation and a set of written internal rules that regulate its operation and define responsibilities, quality policy and health and/or scientific goals.*

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\(^4\) The expression “source subject” is usually used in preference to that of "sample donor".

It is necessary for a biobank to have a delimited physical space, structure, organisation, scientific management, and an operations rulebook, with allocation of responsibilities, both as regards ensuring bank quality and data protection, and as regards the protocols for incorporation and withdrawal of samples, and for release of samples to researchers at external institutions, be they public non-profit or private-sector institutions. The latter includes release of samples to researchers from other countries, in accordance with any possible international regulations (where these exist) and general biobank policy.

Researchers must request authorisation for the establishment of the biobank, and institutional support for maintenance of the security of the samples and databases in line with prevailing legal requirements. Authorisation must imply the availability of adequate finance.

In the interests of quality, and before embarking upon the collection of samples, Standardised Work Procedures must be established for: 1) obtaining samples; 2) obtaining and recording data associated with such samples, including the system for collecting and filing informed consent records; 3) storage conditions, including the safety mechanisms to guarantee these, temperature monitoring and recording, and safety devices to ensure that the conditions are maintained uninterruptedly; and 4) conditions for the dispatch of samples and accompanying shipping documentation.6

Likewise, safety mechanisms must be put in place to ensure the confidentiality and long-term maintenance of the database in accordance with prevailing legislation, with the relevant protocol being duly drawn up.7, 8

The institution housing the collection or biobank is liable for its custody. Custody implies responsibility for the security and safety of the samples stored, safeguarding donors' interests, and ensuring control over the use and availability of both samples and results. Accordingly, more stringent safeguards and protection can be offered with respect to source subjects' rights, and provision made for attending to the necessary formalities in the event of a change of researchers.

6 Royal Decree (Real Decreto) 65/2006 of 30 January, which lays down requirements for the import and export of biological samples.
7 Personal Data Protection Act (Ley Orgánica) 15/1999 of 13 December.
Recommendation 2. Enhanced access to and exchange of information and samples for research should be ensured, provided that confidentiality is protected.

Various international organisations have recommended that samples should be available for the scientific community, and have highlighted the beneficial value of such collaboration. The value of any given collection is proportional to the amount and quality of its samples and related information, and the greatest benefits are to be had from high-quality cooperative research. Hence, provided that confidentiality is protected, fostering access to and exchange of information becomes an ethical imperative. Such activity includes the issue and availability of catalogues listing the samples contained in the biobank. The drawing-up of an annual report of the bank's activities and the research to which it has contributed is a way of formally placing the collection's value, usefulness and ensuing health benefits on record.

Recommendation 3. A biobank should seek the advice of an Ethics Committee, which will ensure compliance with the ethical principles applicable both to biomedical research undertaken in projects that serve to add samples of human origin to the biobank, and to any use that may be made of these.

Both the collection of biological samples for research and the creation of a biobank must be supervised by an independent, multidisciplinary Ethics Committee. Its goal will be to protect the dignity, rights, safety and well-being of the participant subjects, specifically with respect to consent, confidentiality, assessment of the balance between the benefit and risk of the research, and any use to which the material and related data may be put.

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8 Royal Decree 994/1999 of 11 June, governing the regulation of security measures for automated personal-data files.
The Ethics Committee is to issue reasoned reports of its assessments. Furthermore, the Ethics Committee will be able to advise the institution or researchers on changes in regulations and legislation relating to the topic, and on any possible ethical conflicts that might arise as a result of advances in science and technology applied to human beings and the reconciliation of researchers’ and participants’ interests.

**Recommendation 4.** The biobank must avail itself of the services of a scientific committee, which will advise the director on the biobank's management and scientific goals, and draw up the pertinent operating standards. Similarly, the committee will advise on any research activities to be undertaken that are of strategic importance to the optimal use of the biobank, approve any transfer of samples to third parties, and provide guidance on the prioritisation of release of samples.

The institution could consider the possibility of ethical and scientific evaluation being undertaken by a single committee that assisted the biobank's director. Through the actions of an independent body, the ultimate goal would be to ensure respect for ethical rules and responsible management of the samples of human biological material and related databases that go to make up the biobank.

**Degree of identification of samples**

**Recommendation 5:** When it comes to considering the need to establish a newly-created biobank, the degree of identification of the samples must be defined and justified in terms of the collection's designated goals, purposes and end-use. All these aspects should be submitted the Ethics Committee for review.

Samples can be stored with identifiers, using different degrees of identification, or alternatively, without identifiers. Such samples are deemed identifiable in the former and non-identifiable in the latter case.
Identifiable

- **Identified.** The samples retain a personal identifier, e.g., name, ID number, or social security number. The researcher has access to same and can link the database and research information directly to the source subject.

- **Identifiable/ coded/ reversibly disassociated/ pseudoanonymised.** These are terms used in the bibliography for samples that retain a code linked to identifiable personal information. In those cases where the researcher does not have access to the code but this is instead under a third party's control, the material is termed, “linked anonymised”, which confers enhanced confidentiality protection.

Non-identifiable

- **Irreversibly anonymised/ irreversibly disassociated.** These are terms used for samples in which -whether per se or in combination with other related data- it has been rendered impossible for the source subject to be identified as a result of a reasonable effort. Such samples are also termed, “unlinked anonymised”.

- **Anonymous.** These are samples that are initially collected without personal identifiers and thus retain no link with the subject's identity.

Although biobanks with anonymous data and non-identifiable samples are more manageable and, in principle, pose fewer ethical problems, for certain types of research, such as epidemiological research or the study of given hereditary diseases, the retention of personal identifiers may nonetheless be necessary or convenient. Keeping samples with links to personal, medical or lifestyle data for research purposes may require identifiers to be retained in order to make biomedical research more effective, since this would enable source subjects to be contacted, not only to gather new information but also to link such information to other records. Furthermore, subjects could benefit from research results, where these lead to new therapeutic or preventive options. In such a situation, the storage of samples linked to personal health data makes it essential for maximum protection to be ensured, so as to safeguard the confidentiality of source subjects.

Hence, any decision to remove identifiers irreversibly calls for careful consideration of the benefit-risk relationship because, while there are demographic and clinical data that may accompany an anonymised sample, future research proposals may nevertheless be rendered unviable due to the absence of sample identifiers. Should the decision be taken...
to anonymise the sample irreversibly, the procedure must then be standardised and protocolised. Both the anonymisation process and the use of non-identifiable samples should also be subjected to an ethical review, since research with non-identifiable samples is not exempt from a bioethical dimension. Moreover, if such samples were to belong to a group or community that was identifiable as such, this would be particularly relevant in view of the harm that could ensue from their use.

Safeguards for biobank data-management

Recommendation 6: Biobanks must organise an information system and relevant security protocol which ensure that source subjects’ personal data, health data and data drawn from research results are protected in accordance with the prevailing legal regulations, with the confidentiality of the data being guaranteed at all times.

Before embarking upon sample collection, the information to be gathered and the format (manual and computerised) used to store sample-related information must be defined. Both must be guided by respect for the subject’s autonomy, right to privacy and confidentiality of data envisaged under the legal regulations currently in force. It is therefore necessary for the biobank to draw up a protocol outlining the appropriate measures for ensuring compliance, and laying down the chain of custody of the samples and related database, and any restrictions on access to same. Similarly, provision must be made for measures to ensure compliance with the rights of objection, rectification and cancellation.

Consent to participate in research and have samples incorporated into a biobank

Recommendation 7: Incorporation of prospectively collected biological samples into a biobank and their use for research require the subject’s informed consent. Omission of informed consent must be an exception and must, in all cases, be approved by an Ethics

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14 Act 41/2002 of 14 November, the basic enactment governing patient autonomy and rights and obligations in matters of clinical information and documentation, Personal Data Protection Act 15/1999 of 13 December and Royal Decree 994/1999 of 11 June, governing the regulation of security measures for automated personal-data files.
Committee. Subjects must be made to understand that their samples are to be used for research purposes.

Informed consent is necessary for participation in research, incorporation of samples into a biobank and their subsequent use in research.

Researchers must in all cases ensure that source subjects receive the appropriate information and understand that the sample collected is to be used for research and not therapeutic purposes, so that no personal benefit will be had from its donation. Source subjects must also be informed that they retain their rights over their samples and data, that confidentiality in the handling of same is guaranteed, and that the projects in which their samples are involved will be evaluated and approved by an independent Ethics Committee.

In exceptional circumstances, e.g., when historical samples are incorporated into a bank, these can be used without the subject's prior consent, though always under the supervision of an Ethics Committee (also see recommendation 16 on post-mortem samples).

Recommendation 8: Once granted, informed consent may be extendable for use of samples and related data in subsequent research, for purposes compatible with those of the project for which they were collected. Nevertheless, researchers would have to offer subjects the opportunity of choice with respect to any subsequent use of their samples.

Stored samples may be used in research conducted at a later date, provided that the aims pursued are compatible with those originally designated. To this end, it is essential that source subjects be able to choose with respect to any such subsequent use. The researcher can offer subjects diverse possibilities, such as: a) having the option to refuse consent for secondary uses; b) permitting any use, but only in cases where the sample is irreversibly anonymised; c) permitting research relating exclusively to a given disease or diseases; d) consenting to the sample being kept, subject to the condition that, if it were to be used in another project, specific consent would be sought; and, e) having the option to grant blanket consent for the use of samples.

Although blanket or generic consent for future research use of prospectively collected samples that retained their identifiers might be inappropriate, it could nonetheless be sought in special circumstances (e.g., in cases of reuse of samples kept for diagnostic
confirmation, where subsequent use for research purposes would represent a benefit for society, yet recontacting source subjects would entail an excessive workload or additional funding).

Recommendation 9: The process of obtaining informed consent requires: complete, specific and suitably adapted information; comprehension of the information; and a freely given, voluntary, express, specific and documented grant of consent by the participant.

The creation of the biobank, as well as its possible uses for future research, must be undertaken with the participants’ free, voluntary, express, specific, informed and documented -normally, written- consent. Only in given exceptional situations can this be done without the subject’s prior consent.

Source subjects or their legal representatives (see recommendation 10 addressing research on vulnerable subjects) must be informed about the samples to be stored and the data to be recorded, and this information must be supplied individually, be specific to each research project, and be suitably adapted to the individual subject's comprehension ability and cultural characteristics.

Researchers must ensure that, before giving consent, the source subject has understood the information furnished to him/her.

Members of staff who access the data in the performance of their professional functions are subject to the duty to respect confidentiality. The researcher or institution responsible must ensure that all such staff members are conversant with these obligations.

The source subject must receive a copy of the briefing documents used and a signed copy of the consent given.

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16 Disclosure of professional secrets is defined as a crime under Article 199 of the Penal Code. In addition, Article 5, subsection 4 of the Biomedical Research Bill (Proyecto de Ley de Investigación Biomédica) 121/104, lays down that “any person who may, in the performance of his functions in connection with medical-healthcare or biomedical research whatsoever the scope thereof, have access to personal data, shall be subject to the duty of secrecy”.
Recommendation 10. Research may be conducted on vulnerable subjects (in particular, minors or those lacking capacity to give consent) provided that: the research results are likely to be of direct benefit to the participants’ health; such research may not be conducted on other subjects capable of giving their consent; and, the legal representatives of the intended participant have given their written consent. Where the person lacking capacity is an adult, he/she shall participate in the consent procedure to the extent that this is possible. Likewise, account is to be taken of the opinion of minors, in accordance with their age and degree of maturity.

Prospective samples are to taken from children or other vulnerable subjects only where the results of the research are likely to yield a direct benefit vis-à-vis the participant's health, because in such cases the duty of protection must take precedence over the possibility of obtaining valuable knowledge.

The general criterion to be followed is that of “minimum risk”, with this being construed as the risk that anyone would assume in his/her daily life and activities. This in turn means that any research which exceeds this minimum level of risk, may only be undertaken if the benefits to be obtained can be expected to offset the risk, and if such benefits will be for the source subjects. This minimum risk must be evaluated by an Ethics Committee, having reference to all the information available and weighing up the circumstances.

In exceptional cases, where it is not foreseeable that the research results will have a direct benefit on the participant's health, a research project could be authorised when it is aimed at contributing to the enhancement of scientific knowledge about the individual's disease and obtaining results that might afford benefits for other persons who are of the same age or suffer from the same disease, provided that such knowledge cannot be obtained through other subjects capable of giving consent.

The informed written consent of the legal representatives is required. Where the person not having capacity is an adult (over 16 years of age), he/she is to participate in the authorisation process to the extent that this is possible. Similarly, account is to be taken of the opinion of minors, in accordance with their age and degree of maturity.\textsuperscript{17, 18}

\textsuperscript{17} Additional protocol to the convention on human rights and biomedicine concerning biomedical research. Chapter V. Council of Europe. ETS No. 195. Strasbourg, 25. I. 2005.
Recommendation 11: The informed consent document must be drawn up. This is to include the consent form and information sheet, both of which must be submitted to an independent Ethics Committee for discussion and approval.

In line with the nature of the information (see recommendation number 8 on blanket consent and subsequent use of samples), the informed consent process is to be set out in a document that must include the form and information sheet on consecutively numbered pages. At minimum, this document must include the following aspects:

1) the purpose and goals of the research project;
2) the potential that the material provides for research;
3) the purpose and goals of the biobank;
4) the procedure and risks associated with the taking of samples;
5) the duration of storage and availability of the sample, once the agreed storage period has expired or in the event of the source subject's death;
6) the institution entrusted with the custody of the biobank;
7) the identity of the researcher and biobank director;
8) the variables to be recorded in the related database;
9) the individuals' right to express their wishes as regards consent for future use of the samples or data for research. Subjects would be entitled to stipulate restrictions for the use of their samples;
10) possible release of the samples and data to other researchers and, where applicable, the conditions for such release;
11) the safeguards for maintenance of confidentiality of any information obtained. Source subject are to be informed regarding any persons who will have access to personal data (e.g., researchers, health professionals, etc.);
12) the right to revoke consent at any time;
13) the right to be informed about the possible elimination or irreversible anonymisation of the samples and data;
14) the individuals' right to decide whether or not they wish to receive information on such research results that concern them and, if so, who, when and how they are to be informed;

18 Act 41/2002 of 14 November, the basic enactment governing patient autonomy and rights and obligations in matters of clinical information and documentation.
15) the possibility that commercial use will be made of material and data, including the results of such research,\(^{19}\) and that the source subject will not receive any financial benefit;
16) should it not be possible for research results to be published without identifying the person who participated in or furnished biological samples for such research, the results shall only be published where there has been prior consent thereto;\(^{20}\)
17) the expected benefits, if any, for source subjects and their families from their participation in the research, and the risks;
18) the benefits for science and their possible healthcare repercussions;
19) subjects' rights of objection, rectification and cancellation with respect to their data in accordance with prevailing legislation, as well as their right to request the sample's removal or destruction; and,
20) the guarantee that the project has been duly evaluated and approved by an Ethics Committee.

**Recommendation 12:** Source subjects have the right to withhold their consent to participate and to revoke consent given at any time, without giving explanations of the reasons, and without incurring penalisation of any type.

To withhold or withdraw consent to participate in research or have a sample included in a biobank is the every source subject's right and, thus, may in no case give rise to any form of discrimination against him/her and, in particular, against his/her right to healthcare.

In those cases in which there may be justification for scientifically analysing the reasons for not participating, any request for information about such reasons must be made subsequently, so as to avoid influencing the decision.

Revocation by a patient of informed consent in respect of a sample included in a biobank will lead either to the destruction of same or, alternatively, to the elimination of any identifying element, thereby anonymising the sample, without prejudice to the preservation of data resulting from any research that may have been previously conducted.\(^{21}\)

\(^{19}\) Pursuant to Directive 98/44/CE of the European Parliament and of the Council of 6 July 1998, on the legal protection of biotechnological inventions, consent is not a requirement of patentability, but whoever takes a biological sample of human origin must disclose its destination (Recital 26 of the Preamble).
\(^{21}\) Bill 121/104, Article 60.3
question of which of the above two criteria is the more suitable in the circumstances will be for an independent Ethics Committee to decide.

**Recommendation 13. In the case of samples obtained for healthcare purposes (whether for diagnostic ends or via other health interventions), their incorporation into a biobank and possible future use in research require the necessary informed consent. This can be sought simultaneously, albeit in a specific and differentiated manner, with consent for the performance of tests or interventions.**

Biological samples obtained for healthcare purposes, such as those obtained for genetic testing of different types (invariably DNA, live cells, whether cultivated skin fibroblasts or immortalised lymphoblast cell lines) or those obtained from population screening, such as samples left over from neonatal screening, are very valuable scientific material, and destroying them on conclusion of the healthcare process may entail a considerable loss.

The individuals from whom the samples/data have been obtained must be informed of the latter’s possible storage and subsequent use in research, and their consent to and the conditions upon which these two goals may be attained must be sought and agreed\(^\text{22, 23}\) (see recommendation 7 on the requirements for obtaining informed consent).

This recommendation refers to biobanks that have been prospectively built up. For management of historical collections, kindly also see recommendation 16 on post-mortem samples.


Right to know and right not to know

Recommendation 14. Source subjects must be informed of the results of the research and also, where applicable, of the possibility that unexpected findings may be made in the course of research. Subjects must be offered the possibility of deciding whether or not they wish to receive this information.

The fostering of patient autonomy, a factor that underlies obligations relating to information and informed consent in all research on human beings, includes: on the one hand, the patient's right to know the research results (both expected and unexpected), which in turn entails the researcher's duty to offer such information\(^\text{24}\) (see point 14 of the explanatory part of Recommendation 11 on the wording of the informed consent document); and, on the other, consideration of the subject's possible legitimate interest in not wishing to know certain information, such as genetic information obtained from research (ranging from information on discordant paternities to advance knowledge of incurable diseases). An instance of this would be to prevent adverse psychological and major undesirable consequences, particularly where the information were not associated with the ability to alter the circumstances or failed to represent a possible direct advantage for the subject, or alternatively, where the information obtained in the research might be somewhat inconclusive or less than 100% predictive. This consideration has come to be termed the "right not to know".\(^\text{25}\)

There is no automatic presumption of this "right not to know". Instead, the affected party must expressly choose to "activate" it. In view of the fact that information which affects an individual, may not do so exclusively and may thus be of potential interest to third parties (family or friends) who have not participated in the study, this right is not absolute and can


\(^{25}\) In this respect Article 4, paragraph five of the Biomedical Research Bill states: "Respect shall be had for the right of any person to decide that he shall not be informed of data to which the foregoing section refers (genetic and other data of a personal nature), including any unexpected discoveries that may come to light. However, where such information should be necessary to prevent serious harm to his health or that of his biological relatives, a close relative or an authorised representative shall be informed".
be restricted where the aim is to avoid a relevant risk to third parties. In this respect, the “right not to know” is not equivalent to the “right to know”.

The disclosure of results of genetic research is paradigmatic of such situations. In addition to the above, the often ‘translational’ nature of research, the development of pharmacogenetics, as well as retrospective research on samples drawn from historical banks, which can produce results of interest to the families many years after being collected, may be a source of ethical problems.

Accordingly, all these considerations must be systematically evaluated, not only by biobank management, but also by researchers and Ethics Committees, when it comes to drawing up the protocols, work procedures and pertinent informed consent procedures. A good solution is for researchers to adopt an a priori criterion as to whether or not unexpected discoveries are to be disclosed, regardless of whether such discoveries may or may not have a direct bearing on the source subject's health, and submit this to the Ethics Committee for consideration, particularly insofar as the principle of non-maleficence is concerned.

Should it prove possible to foresee or predict the type of discoveries that may be made in a prospective research project, it would be advisable for this matter to be agreed with the subject beforehand. In retrospective research, the criteria to be followed must be established previously and submitted to the Ethics Committee for review.

As in routine healthcare procedures, in any case where research might include genetic testing, the information and disclosure processes should be take place within a genetic counselling context.

Consent for release of samples to third parties

Recommendation 15. Where applicable, release of samples to third parties should take into account the conditions agreed in the informed consent. In all cases, release of samples for other research is to be evaluated by an Ethics Committee, which will consider the project's scientific validity, as well as the need, if any, for renewal of consent to be sought.

The criteria for release of samples to third parties are to be stipulated in the procedure for obtaining informed consent. The principal researcher and the institution are responsible for
custody of samples and for safeguarding the interests of source subjects. Hence, they should draw up a global policy for release of samples, considering that:

1) samples are only to be released when the applicant researcher submits a research project approved by an Ethics Committee;

2) the Ethics Committee of the institution housing the biobank is to evaluate such projects for which release of samples (and related data) is sought, and shall, where applicable, approve the release of the samples and demand compliance with the conditions agreed upon in the informed consent document or renewal thereof (see recommendation 7 and explanatory text); and,

3) a balance is to be sought between development of research and maintenance of the biobank's scientific value. In this respect, the scientific committee may advise on release priorities in the event of any conflict.

Taking of post-mortem samples

Recommendation 16. For extraction of biological matter from a deceased person for research purposes, account is to be taken of appropriate previous consent given by the subject or, where this is lacking, by his/her relatives or legal representatives. No samples are to be taken from a deceased person for research if the deceased person is known to have objected to it.26

Under Spanish law, body organs or other anatomical specimens may be extracted from deceased persons for therapeutic or scientific purposes, in any case where such persons have failed to leave an express objection thereto on record.27,28 Nevertheless, a good practice from an ethical standpoint is to seek informed consent from relatives or legal representatives to biological samples being obtained from deceased persons and preserved for research purposes.

Furthermore, relatives should be apprised of and consulted on the possible implications for their interests of any research done on identifiable samples. They must also be

27 Organ Transplant and Extraction Act 30/1979 of 27 October. Article 5.2.
Management of historical collections of biological samples

Recommendation 17. Historical collections of biological samples obtained for healthcare or research purposes must meet the established requirements and recommendations for setting up a new biobank, with the new samples being incorporated subject to the necessary request for informed consent. Conditions laid down for retrospective use of samples require evaluation by the Ethics Committee.

When identified or identifiable sample are to be used, researchers must recontact the source subject in order to seek new consent, except where the Ethics Committee deems that there are special circumstances for exemption, with the necessary precautionary measures being taken.

Post-mortem samples are to receive the same consideration.

It is commonplace for hospital diagnostic departments to house a great number of stored human biological samples which were collected for healthcare or research purposes and stored without informed consent being sought. In such cases, the advisability or inadvisability of preserving these historical samples will have to be assessed, taking into account their scientific value and the difficulties of bringing together collections in some cases (e.g., rare diseases), provided that the terms of use are regulated and the relevant ethical and legal aspects are borne in mind.

Collections of anonymous or irreversibly anonymised samples do not pose special problems of use, since they could hardly harm source subject if they are unidentifiable.

In the case of existing non-anonymous or non-irreversibly anonymised collections, researchers should make a reasonable effort to contact the source subjects, in order to obtain new consent for the projected study. However, this measure may be impracticable.

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28 Royal Decree 411/1996 of 1 March, governing activities relating to the use of human tissue. Article 8.
either because it calls for a disproportionate effort or invalidates the study as a result of selection biases being introduced, or because it could cause psychological harm to the extent that the subject is made to relive a painful personal or familial situation. In such cases, an Ethics Committee could evaluate and, where applicable, approve the use of biological samples without specific consent, on condition that the following requirements were met, namely: that the proposed research is of relevant scientific interest; that the samples are necessary for the attainment of the research goals; that there is no evidence to show the source subject would have raised any objection to the sample being used for research; and, finally, that the research will in no way prejudice the source subject's interests.

In collections of historical samples, it is possible that some of the source subjects may have died. This fact cannot justify a policy of unrestricted access on the grounds that there is no longer any risk or harm for the individual, for the simple reason that, if research on post-mortem samples were to involve relevant information about live relatives, this could prove harmful to them.

If an individual restricted the use of his/her samples for research when he/she was alive, these restrictions will continue in force after his/her death.

Ownership and marketing of samples and research results

Recommendation 18. Surrender of samples by source subjects must be without financial consideration. Neither source subjects nor their family or friends are to obtain financial benefit from the surrender of the sample, or any commercial benefits that might flow from the results of the research.

There are two reasons to justify why surrender of samples should be disinterested: the first of these is the conviction, present within our cultural context, that organs and tissue, including blood, should neither be bought nor sold,29 since it is thought that the human body and its parts shall not, as such, give rise to financial gain", Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine: Convention on Human Rights and Biomedicine. Council of Europe, 4 April 1997. Article 21.

body should not be the source of financial gain, since this would mean treating persons as objects and so violating respect for their dignity.

The second reason is as follows: source subjects give their sample voluntarily and retain certain rights with respect to the sample and its destination. The act of surrender is not exactly the same as the act of donation, yet the principle governing surrender of samples is the same as that relating to donation of organs, i.e., disinterested and altruistic solidarity. The source subject offers a valuable asset for science and society, in most cases without seeking to obtain personal therapeutic benefit. No financial benefits are to be had, since this would nullify the act of surrender-donation. Yet, this is no bar to the person from whom the sample has been extracted being entitled to receive compensation for any expenses he/she may have incurred or any losses that he/she may have suffered, provided that such compensation does not constitute remuneration.

In contrast, technical tasks such as the taking of samples, storage, etc., may indeed give rise to a legitimate and reasonable remuneration for the biobank. In this respect, it would also be licit for the biobank to receive compensation for the costs of collection, storage and dispatch of samples where these are requested by third parties (release to other researchers, pharmaceutical companies, etc). However, to delimit this practice in a satisfactory manner is difficult and so, with the aim of achieving a balance that would be fair for source subjects and any possible benefits that third parties might obtain, it would be desirable if consideration were instead given to the avenue of shared enjoyment of benefits (see recommendation 19 on return of benefits to the community).

Insofar as the results obtained from research are concerned, the ensuing benefits (stemming from the marketing of a drug or its by-products) are deemed to correspond to those who promote or conduct the research. The source subject of the sample used in the research should neither receive any financial benefit nor have any legal right over such research. It is advisable for source subjects to be informed of this aspect in the context

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30 Article 7 of the Biomedical Research Bill lays down that “Donation and use of human biological samples shall be free of charge, whatsoever the specific origin thereof, and in no case may the compensation envisaged hereunder assume a lucrative or commercial nature. Donation likewise implies waiver on the part of the donors to any right of a financial nature or of any other type over such results as may directly or indirectly flow from research undertaken with said biological samples”.

of procuring informed consent (see recommendation 11 on the information to be given in the process of obtaining consent).

Return of benefits to the community

Recommendation 19. The ultimate aim of any benefits yielded by the results of research based on biological samples is the improvement of the community and shared enjoyment of such benefits should thus be sought. Return of benefits to the community is a response to the principles of equity and justice.

In order to achieve an equitable balance between source subjects and third parties (pharmaceutical, biotechnological and other companies), and as the key to the moral legitimacy of research, the most appropriate thing would be to endeavour to ensure shared enjoyment of the benefits,\(^{32}\) which may take any of the following forms:

- special assistance to the persons and groups that have taken part in the research;
- access to medical care;
- provision of new diagnostics, facilities for new treatments or drugs stemming from the research;
- support for health services;
- capacity-building facilities for research purposes;
- preferential access to therapies developed as a result of their contributions to the biobank; and also,
- participation in therapies in line with the principle laid down by the Human Genome Organisation (HUGO) Ethics Committee in its Statement of Benefit-Sharing, which requires investment of 1% to 3% of net research earnings in public foundations, e.g., in the expansion of medical or humanitarian aid infrastructures.

Knowledge obtained through research is a benefit for the community and an asset that, in all justice, should be shared and should contribute to humanity as a whole. Hence, the results should be published without any undue delay, disseminated critically and supported by the appropriate documentation. It is advisable for the principal results to be

\(^{32}\) As stated in this regard by the HUGO Ethics Committee and UNESCO in its International Declaration on Human Genetic Data, specifically at Article 19, on laying down that “In accordance with domestic law or policy and international agreements, benefits resulting from the use of human genetic data, human proteomic data or biological samples collected for medical and scientific research should be shared with the society as a whole and the international community.”
published in a way that ensures they reach the study participants and other interested members in the community in which the study was conducted.\textsuperscript{33}

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