



Review Article

Biobanks and Their Importance in the Clinical and Scientific Fields Related to Spanish Biomedical Research ☆



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ABSTRACT

The reality of biomedical research in Spain requires having an updated knowledge of the research reality and its ethical/legal framework. Research studies with human biological samples should be made with a sufficiently large number of samples to reflect the diversity of the human population, which meets the standard requirements to ensure optimum quality of the research results for further development. Furthermore, research with humans and obtaining and/or deriving human biological samples and clinical research studies information are subject to a number of legal requirements and restrictions. Biobanks and biobank networks are established as the optimal structures that favor the storage of large volumes of human biological samples based on criteria to ensure their optimum quality, harmonization and security, respecting at all times, the ethical and legal requirements guaranteeing the rights of citizens.

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Biobancos y su importancia en el ámbito clínico y científico en relación con la investigación biomédica en España

RESUMEN

La realidad de la investigación biomédica en España, exige tener un conocimiento actualizado de la realidad investigadora y de su marco ético/legal. Los estudios de investigación con muestras biológicas humanas deben realizarse con un número de muestras lo suficientemente amplio para reflejar la diversidad de la población humana. Asimismo, deben cumplir los requisitos estandarizados de calidad óptima para garantizar los resultados de la investigación a desarrollar. Además, la investigación con seres humanos, y la obtención y/o derivación de muestras biológicas humanas e información clínica a estudios de investigación, está sujeta a una serie de requisitos y restricciones legales. Los biobancos y las redes de biobancos se constituyen como la estructura óptima que favorece el almacenamiento de grandes volúmenes de muestras biológicas humanas gestionadas en base a criterios que garanticen su óptima calidad, armonización y seguridad, respetando en todo momento los requisitos éticos y legales que garantizan los derechos de los ciudadanos.

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Palabras clave:

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Introduction

We are part of an increasingly aware society regarding the importance of biomedical research to improve health. Therefore, studies related to biomedicine have increased exponentially over the years, creating the need to coordinate basic with clinical studies,

which has fostered the emergence of cooperative models, a fact that has been called translational research. This type of research should be done with biological samples and associated clinical information, ensuring patient safety, quality of care and data confidentiality, with the main objective of achieving more efficient health care.

Promoting translational research and the application of advances in knowledge and technology from research and innovation requires easy access support infrastructure to facilitate quick experimental demonstration of a hypothesis or testing of a previously simulated model. Among the many existing biomedical and health platforms, biobanks are one of the most attractive alternatives, contributing to building bridges between basic, translational and clinical research and clinical practice. These

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establishments have been defined by the Law on Biomedical Research (LIBM), Law 14/2007 of 3 July,¹ as “public or private nonprofit establishments, hosting a collection of biological samples designed for diagnostic purposes or biomedical research and organized as technical units with quality criteria, order and purpose”.

Biobanks and Biomedical Research

What Are Biobanks?

Biobanks are storage banks for samples of human origin, for use in national and international research in the field of biomedicine.²

The constitution of biobanks derived from a number of situations that have occurred in biomedical research in recent decades could be summarized in the following points:

- For the success and development of biomedical research studies, it is currently of great importance to have large quantities of representative samples of biological tissues, tumors, cells, proteins, DNA and other vital fluids including blood, serum, urine, etc.
- Advances in the different techniques called ‘omics’ (genomics, proteomics, etc.) help in obtaining a large amount of data, needing not only high sample but one that ensures quality is preserved in excellent condition and is readily available.³
- The increasingly abundant and close collaboration between different laboratories located in different countries makes sending samples to each other something ever more frequent and leads to a necessity for complete control over the transit of biological material necessary to research.⁴

Therefore, at present, to support and promote biomedical research, excellent biobanks have been established,⁵ with human biological samples linked to human disease diagnosis, samples of ‘healthy individuals’, etc. from which further biomedical research can develop, taking into consideration the criteria to ensure the quality and suitability of biological samples collected and stored,⁶ and respecting at all times, the ethical and legal requirements that guarantee the rights of citizens.

The main purpose for which biobanks have been established is to empower those biomedical studies considered particularly relevant, focusing on the analysis and improvement of knowledge of conditions or diseases including cancer, infections, ‘rare’ disease, etc., where there is need of a large sample, to obtain certain demographic characteristics of the samples, social and food habits, environmental characteristics of the patients’ living environment, etc.

The main distinguishing feature of biobanks, as currently understood, from the classical concept of collection of samples and associated data (collection of a research group, institutional collection or private collection), is committed to the transfer of samples and information associated with them to the research groups in an open, transparent and generous manner, benefiting science and, above all, patients.

How do Biobanks Work?

The operation of biobanks focuses on managing, under the criteria of safety, quality and efficiency; the receipt, processing, storage⁷ and subsequent transfer of samples to researchers for use in their research projects, provided that these studies met all applicable ethical and legal requirements for such activities.

All biomedical research requires collecting data and biological samples of people affected by a disease, as well as people not affected by the disease, to analyze and draw conclusions for improving knowledge and advancing the diagnosis and/or

treatment of diseases under research. The samples for the disease diagnosis or control, once employed for this purpose, are also useful and necessary for research. In fact, many of the scientific advances made in recent years in medicine are the result of such studies. In this context in which current and future biomedical research is structured, biobanks are established as the most suitable organization to save and provide the scientific community with samples that initially had been obtained for other purposes and whose leftovers are useful for biomedical research.⁸ The samples and associated information should be stored in the same areas established for this purpose, within the premises of the health center involved, under the responsibility of its management.

The human biological samples and associated data sometimes include genetic information, which must undergo security measures established by specific legislation regulating the protection of personal data.⁹ Other issues include the assignment of samples and data associated to community researchers (member countries of the European Union) and other researchers (non-members) which shall be made in a non-identifiable way, i.e. the sample only associated with generic and coded data, which will prevent the researcher from knowing the identity of the person from which they come. All of them will be required to ensure that they will work with the same level of protection required by Spanish legislation regarding data.

On the other hand, it is noteworthy to indicate that any project in which human biological samples are employed must be previously authorized by the relevant ethics committee. A necessary prerequisite for biobanks to provide samples is the need for prior favorable assessments by external Ethics and scientific committees.

The mass storage of biological samples raises complex technical issues that affect sample collection, transportation, identification, traceability, storage at different temperatures, the recovery of the stored sample and the processing of the data, etc. All these aspects show that to make the existence of such establishments efficient, four fundamental tasks must be developed,¹⁰ such as the standardization of the protocols used, the establishment of an appropriate methodology for coding and identification of samples, a rigorous informed consent and a well qualified staff.

Regulations Governing the Use of Human Biological Samples in Research

All research involving human subjects, or involving the collection and/or derivation of human biological samples and associated clinical information, is subject to certain requirements and restrictions provided by law, responsible for its development, which should be taken into consideration to avoid committing actions that do not comply with the legal premises, and which carry penalties on the direct perpetrators and their collaborators.

The different legislation governing research in humans is centered on the respect and protection of constitutionally recognized principles such as: the integrity of persons, protection of human dignity and the protection of human identity.

Therefore, and in order to regulate and promote properly these and other practices, in 2007 the LIBM, and later, in 2011 the *Royal Decree 1716/2011 of 18 November* were adopted, which establish the basic requirements for authorization and operation of biobanks for biomedical research and treatment of biological samples of human origin, and the operation and organization of the National Registry of Biobanks for Biomedical Research (1716 RD)¹¹ is regulated, and constitutes the policy document established to develop the basic precepts contained in the LIBM, regarding the use of biological samples for scientific and technical research, including innovation and development for the primary or secondary purpose of obtaining, storing or assignment thereof.

The RD 1716, in its introduction, states that the rights of individuals shall be respected provided their biological material is used to obtain new scientific knowledge, confirm hypotheses, or engage in technological upgrades, quality control, teaching, etc. and distinguishes between a general scheme for the treatment of biological samples for biomedical research and the specific measures to be applied when this treatment is carried out in a biobank.¹²

Throughout the development of RD 1716 along with its provisions, principles and premises regulated by LIBM remain, and different objectives are set, highlighting the main aspects of the most important items:

Collection Regimen, Storage and Use of Biological Samples of Human Origin

The biological samples of human origin to be used in biomedical research may be stored in a biobank or collected for biomedical research outside the organizational level of a biobank or stay preserved for use in a specific research project. In all these cases, it is essential to obtain the informed written consent of the subject source.

Definitions:

- Biobank: public or private property, non-profit, which houses a collection of biological samples for diagnostic purposes or intended for biomedical research and organized as a production unit with quality, order and purpose criteria. By definition, the biobank samples may be used in any biomedical research, provided that legal regulations are met and that the subject source has consented to these terms.
- Collection of biological samples for biomedical research: ordered biological samples collected for special interest or value to biomedical research as a whole. Excluded from this concept are biological samples of human origin that are kept exclusively for a specific research project and are not to be transferred to other researchers. Samples of a collection may only be used for the purpose stated in the specific consent.
- Project with biological samples for biomedical research: research project that retains biological samples to be used exclusively in connection with the project, provided that such preservation does not extend beyond the end date of the trial and the samples will not be assigned to other researchers. Its use in another project or integration into a biobank or a collection requires the written consent of the subject source.

In relation to biobanks, it should be noted that the samples are obtained with a broad consent (without having to specify the purpose) compared to that established for other purposes such as research projects or collections of samples for developing lines of research, where it is necessary to detail the specific purpose for which they are obtained. Biobanks can obtain and retain human biological samples indefinitely, to make them available to the scientific community for use in future research, not foreseen at the time of collection and always respecting the nature of the sample. Samples may be provided for use in scientific and ethically approved research, and such assignments will be made, as a rule, anonymous or dissociatedly, being a prerequisite for the realization of such transfer, establishing an agreement between the parties involved (the project manager of research and biobank) in which the researcher will agree to not to give the samples a different use than that for which they were requested, and it will be assumed that the samples may not be assigned to any different researchers.

Informed Consent Requirements for Obtaining, Storing, Conserving and Using Biological Samples of Human Origin and Its Associated Data

RD 1716 provides that sample collection, preservation and storage or subsequent use will require specific prior consent of the source subject, in which the purpose of obtaining samples and other information shall be indicated in Article 23 thereof.

If the goals established for samples are several (project, collection and/or biobank), these may appear in the same document, but the power of the source subject to consent for each purpose independently must be guaranteed in every case.

The document attesting the consent of the source subject to the collection and use of their biological samples for biomedical research shall be issued in triplicate. One of these will be delivered to the source subject, another will be kept in the center where the sample was obtained and the third shall be retained by the biobank, or by the person responsible for the collection or investigation, as appropriate.

Consent may be completely revoked at any time or for certain purposes.

Referral to Researchers of Samples Collected for Health Care Purposes

RD 1716 also regulates the use for research purposes of human biological samples obtained in the exercise of patient attention, diagnostics or therapeutics, within the medical care provided to the patient/donor testing. Such samples may lead to research provided the following requirements are met:

- The samples obtained for diagnostic or therapeutic purposes may be used in research if this does not compromise that initial end.
- Whether it is the remnants of those samples, or the same samples after the legal storage term has finished.
- Prior informed consent of the donor and the professional responsible for their care is obtained, to derive these samples for research.

When the donor or the donor's family need to use the sample donated for health reasons this will always have priority, if the sample is available and not anonymized.

Regular Operation and Organization of the National Registry of Biobanks for Biomedical Research

This registry is a body that is established for the purpose of nationally regulating the storage of human samples for research, and making known to the scientific community and the general population, the collections of human biological samples that exist in our country and are intended to be used in the development of biomedical research.

All collections and biobanks must be enrolled in the registry and all data must be available to the public. Thus, any researcher, regardless of their location in the country, wanting to develop a research project that needs to use human samples, once approved by the appropriate ethics committee, can access the information center and may apply to biological material required for their research.

Role of Biobanks in Rheumatology Research

In the area of rheumatic diseases, as in most research in biomedicine, for any research project to be performed properly, it is essential to use high-quality biological samples associated

accurately with clinical information, and meet the highest ethical standards and patient autonomy required by law. Moreover, in this area as in other fields of research, we are witnessing a major change in the way research is done, evolving from an individual to a cooperative research investigation, which involves sharing samples and associated information, not only in terms of efficiency but also respecting the legally established premises.

Until now, the absence of adequate structures has generated great fragmentation and an improved efficiency in the collection and storage of samples, as well as in obtaining related information. This has caused many sample collections associated with various rheumatic diseases to have been collected over many years by different technicians, following different protocols based on various work and storage conditions, which has led to collections of samples of very uneven quality.

All these above mentioned problems could be solved if we had structures that enhance the individual ability of groups to tackle more ambitious scientific projects, or the development of cooperative research. In this sense, the creation of well-structured sample biobanks associated with rheumatology patients can be very helpful for the development of these projects, providing support for major scientific achievements and helping to adapt the research developed to current legislation.

Rheumatology is dedicated to a wide range of diseases,^{13–15} most of unknown etiology and pathophysiological mechanisms which are not well defined. The current classification of these diseases is purely clinical (signs, symptoms, progression, etc.). It would be necessary to try to develop an etiopathogenic or pathophysiological classification using genetic studies in phenotypically well defined patients. The possibility offered by biobanks to count on samples from each patient in different formats (solid, liquid) and at different times of the progression of the disease (diagnosis, progression, pre or post-treatment, etc.) may help to elucidate the mechanisms involved in various pathologies associated with this branch. For example, using different approaches, such as genomics and proteomics, researcher can identify biomarkers of these processes and help design new target molecules for the development of drugs and therapeutic alternatives.

Biological samples from biobanks, which provide top quality genetic material, are an important tool in the elucidation of the molecular mechanisms that promote rheumatic diseases, including epigenetic modifications or interaction between genes and proteins. This genetic contribution is one of the most important factors that play a major role in the risk of developing some rheumatic diseases.¹⁶ In this sense, for example, large population DNA banks can provide valuable information on the prevalence of germline mutations associated with the development of certain types of disease (biomarkers of susceptibility).¹⁷

Proteomics is a discipline that has aroused great expectations in biomedical research for its potential application; first, it can help in the identification of specific biomarkers for diagnosis, classification, prediction and, on the other hand,¹⁸ may contribute in defining new therapeutic targets. These techniques allow for the simultaneous analysis of multiple markers and may become a powerful tool for both biomarker discovery and validation. In that sense, one of the most ambitious projects on a global scale is the human proteome project, in which the role of biobanks can be critical in obtaining quality samples in sufficient numbers.

Research on biomarkers in rheumatic diseases in general is complex since the danger of identifying protein associations with diseases which may prove to be false is high. Therefore, research has to include well designed validation studies to determine the applicability of the genomic and proteomic biomarkers in clinical practice. Their identification may allow an earlier diagnosis, better prognosis and application of specific treatments in what has been called personalized medicine, defined by the design of

drugs targeting a specific molecular target that allows for safe and efficient¹⁹ individualized therapy. Biobanks play an important role in biomarker research and contribute to the development of this new personalized medicine.

Conclusions

The scientific developments that have been occurring over the past few years have revealed to us the need for suitable biological material for the conduction of research, and it is necessary to facilitate access by researchers to large numbers of biological well documented samples, selected with appropriate scientific criteria in order to develop research.

Research studies with human biological samples should be made with a number large enough to reflect the diversity of the human population and meet a standard of quality, to ensure that the samples used in research are developed in optimal conditions for use in research. Generally, however, the collection of significant numbers of human biological samples and information quality is a major effort of planning, construction and finally operation, consuming significant time, which slows the development of experimental research. Therefore, the promotion and operation of biobanks in which the researcher is given access to samples and associated quality data when presenting a project within an appropriate scientific institution, and with an appropriate ethical and legal guarantees for the donor, represent an essential milestone in the shortening of time that usually elapses between research and application of its results, and thus improves the effectiveness of research.²⁰ In addition, these establishments should consider the critical mass of research groups using these resources, the areas in which they work and will work with in the future and seek information, vying to get the resources available in the biobank.

In the area of rheumatology, as in other fields of biomedical research, to advance the understanding of different triggering mechanisms of various diseases encompassed in this area, it is important to have constant coordination and collaboration between and among biobanks with different professionals involved in the treatment of samples and the information associated with them, developing global management of all activities involved: identification and phenotyping of donors, procurement, processing, storage, distribution, sale and use of samples and associated information.

Ethical Responsibilities

Protection of people and animals. The authors declare that no experiments have been performed on humans or animals.

Data confidentiality. The authors state that no patient data appear in this article.

Right to privacy and informed consent. The authors state that no patient data appear in this article

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Conflict of Interest

The authors declare no conflict of interest.

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