THE NEW CONCEPT OF BIO-BANKING: FROM A NATIONAL TO AN INTERNATIONAL PERSPECTIVE

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ABSTRACT

A biobank is a type of biorepository that stores biological samples (usually human) for their use in medical studies. In recent years biobanks have become an important resource in medical research, supporting many types of contemporary research like genomics and personalized medicine.

This study analyzes the legislative and administrative structure that underlies the creation and development of national and European platforms for the storage of human tissues.

This study concludes that the same ethical and legal issues are to be extended to the whole world, and for this reason it is important that these data platforms were known, financed and used in the right way both by the researchers and by the public.

KEYWORDS

Biobank, biological material, sensitive data, translational research, european legislation.

RESUMEN

Un biobanco es un tipo de bio-deposito que almacena muestras biológicas (generalmente humanas) para su uso en estudios médicos. En los últimos años, los biobancos se han convertido en un recurso importante en la investigación médica, que respalda muchos tipos de investigación, como la genómica y la medicina personalizada.

Este estudio analiza la estructura legislativa y administrativa que subyace en la creación y el desarrollo de plataformas nacionales y europeas para el almacenamiento de tejidos humanos.

Este trabajo concluye que los mismos problemas éticos y legales se extienden a todo el mundo, y por esta razón es importante que estas plataformas de datos sean conocidas, financiadas y utilizadas de manera correcta tanto por los investigadores como por el público.

PALABRAS CLAVE

Biobanco, material biológico, datos sensibles, investigación translacional, legislación europea.

1. MOTIVATION

The world of biomedical banks is perhaps the last, but not the least, of the frontiers that the evolution of medicine must face and overcome.

It is clear, in fact, that every scientific progress must correspond to a parallel ability to catalogue, standardize, store and make accessible to all, every type of information available from the scientific and epidemiological point of views.

From this assumption arises the need to create using the scattered and disconnected data already available a new information medium. A "global" biomedical database, in which the most important information regarding the state of "collective health" can be codified and stored ". The potential of a structure that can achieve this is immediately evident, both in terms of the possibility to do accurate statistical research and for the worldwide exchange of scientific research.

However, considering these advantages, it is obviously necessary to pay attention to important ethical and legislative issues:

- the guarantee of maintaining the confidentiality of information, from both an ethical and an administrative point of view

- standardization of collection, cataloguing, storage and availability outside the information collected.

As we know there is no single Europe-wide regulation of biomedical research using human samples and data. For this reason, many countries follow unclear domestic laws, thus compromising the development and quality of research.

At an international level, there are several sources that affect the regulation of biobanks with different legal values, but they are essentially attributable to three institutions: UNESCO (United Nations Educational, Scientific and Cultural Organization) with the Universal Declaration on Human Genome and Human Rights, the Council of Europe end the European Union.

However, these international instruments can only act as a model for national and EU legislation by providing guidelines and best practices developed because of a process of interaction with scientific institutions.

The Oviedo Convention, as a matter of fact, is the only international legally binding instrument on the protection of human rights in the biomedical field.

However, is important to note that some relevant CoE States have still not signed it (such as Germany, Belgium, Austria, the United Kingdom or Russia) while others that have signed it have still not ratified it (Italy, Holland, Norway, or Poland).

Finally, although there are countries that still use unclear internal laws, there are others with well-organized legal framework.

In this context, Spain and Italy can act as opposing examples: Spain has been one of the pioneers in this field because unlike Italy, in which the regulation has been originated from the need to create biobanks to support large-scale projects, Spain prioritized regulating the handling of already existing large collections of biological samples scattered through the network of the National Health Service hospitals, public research institutions, and universities.

The present paper reports European plans current attempts and accomplishments in addressing security ethical and legal problems involved in the creation of biobank data sharing, to ensure donor privacy while promoting scientific advancement using a multilevel prospective to describe the relationship between EU law and national ones.

The paper focuses and analyses specifically the legislative frameworks that apply to biobanking activities to identify differences in legal requirements between Spain and Italy in a broader European framework.

Therefore, it's necessary to make a lot of progress in the development of biobanks. The first step would be the creation of a legal and regulatory assumption that avoiding any possibility of fraudulent use of information allows to make available to all researchers the existing data, beyond the state borders, putting forward the needs of science to improve the health and quality of life of the population.

This document seeks to present an initial analysis of the current situation, at least in Europe, to identify the legal and ethical problems that must be analysed and overcome, and to indicate which are the main differences to amortize and unify. Surely it is not yet possible to present or suggest definitive solutions, but it is certainly possible to highlight the most dissonant themes on which the greatest effort must be focused on for their acknowledgment and overcoming.

2. INTRODUCTION TO THE INSTITUTION OF BIOBANKS

In recent years, human biological material (e.g. tissues, cells, nucleic acids) obtained through common diagnostic procedures has become an important resource for biomedical research (Asslaber et al, 2007).

The promotion of translational research and the application of advances in knowledge and technology derived from research and innovation require the support of easily accessible infrastructures that facilitate the rapid experimental demonstration of a hypothesis or the verification of a previously simulated model. Among the many existing biomedical and health platforms, biobanks are one of the most interesting when they help to establish links between basic, translational and clinical research and health practice (Botti et al 2012).

Progress in genome and proteome research has also allowed us to differentiate multifactorial diseases previously considered as a single disorder into more precise diagnostic entities and DNA has become the starting point for many medical and legal investigations.

This achievement provides the basis for developing a more personalized treatment approach, optimizing clinical protocols and improving disease prevention. However, in order to ascertain the etiology of complex diseases, it is necessary to have access to a wide collection of biological samples with epidemiological, clinical, biological and molecular data from a large number of patients and healthy persons.

The main differential characteristic of biobanks, as they are currently understood, with respect to the classical concept of collection of samples and associated data, is their commitment in the transfer of samples and the information associated to the research groups in an open, transparent and generous way for the benefit of science and, above all, of the patient (Knoppers et al 2012, Moore et al 2011).

The collaboration between different laboratories located inside and outside the countries is becoming increasingly abundant and closer, which makes sending samples from one to another more frequent and requires complete control over the transit of human biological material.

3. GENERAL INFORMATIONS

The term biobank cannot be circumscribed in a unitary concept, but it carries out a complex phenomenology and a multilevel institution.

Because of this, it is impossible to treat indiscriminately any type of biobank, but only the banks of human tissues stored for research purposes.

The biobanks responsible for the conservation of organs destined for transplantation of embryos, spermatozoa or oocytes for assisted procreation are not included in this survey.

These platforms act as links between donors, clinicians, and researchers, with the purpose of assuring efficient management of the stored material.

In the international documents Biobank are defined generally based on the different typology of the preserved samples. According to the roles for the European Biobank of the University of Maastricht, with the term Biobank we intend “an operative unit that supplies a service with conservation and management from the biological material and relative clinical data, in agreement with a code of good utilization and of correct behavior and with further addresses supplied by the Ethical Committees and University” (Zatti, 2011).

The issue of biobanks is very complex because it includes in legal, ethical and social aspects concerning the treatment of data (sample collection, extraction of DNA profile, further processing in database) and for this reason it is a very topical subject. Furthermore, their proper regulation is functional for important purposes:

- the maintenance of the quality of data
- the creation of appropriate security measures
- the safeguard of the right for data subject (including access, rectification or erasure)
- the special provision of trans-border of data flow.

For these reasons Health, Biological and Biometric data are considerate sensitive because they concern the privacy of the person in a different dimension (Sarrión, 2018).

One of the most interesting legal problem derives from the nature itself of human tissues, because they have two indivisible natures: one structural and another genetic (Knoppers, 2000).

So, on the one hand, health data are personal data linked to the health of person, and on the other hand, biological and biometric data can identify the persons. In both case we deal with sensitive and relevant data linked to the privacy (Sarrión et al, 2014).

4. THE ORGANIZATION OF THE BIOBANK

Until a few decades ago, human biological samples were destroyed immediately after their use or their removal from the patient, with the consequent loss of data and information useful for the development of medical science. At best, they were used by the health or by the medical team that had taken care of it for medical research, most of the time without the consent of the patient (Garcıa-Merino et al, 2015).

The use of such biological samples took place to the detriment of both patients, who had no possibility to control the use of their samples, and of the researcher, who did not have the possibility of adequate samples in terms of quantity and quality.

The need to have adequate samples and to circulate the results of research as widely as possible and the related attempt to create some form of harmonization at European and international level have led to the creation of biobanks and the proliferation of agreements or documents dominated by legislation incomplete and indented.

The central points in the European regulatory landscape concerning biobanks are the sources adopted at the international level, which set important principles of reference without imposing binding rules.

At international level, the sources that affect the regulation of biobanks are many with different legal values but essentially attributable to three institutions: UNESCO (United Nations Educational, Scientific and Cultural Organization), the Council of Europe end the European union. These three organizations have different but complementary functions in the field of biobanks and their cooperation has developed thanks to the adoption of numerous legal instruments, at international, transnational and national level.

The first article of the Universal Declaration on Human Genome and Human Rights highlights the relevance of the issue in question by stating that the human genome “underlies the fundamental unity of all human family members” inherent dignity and diversity. In a symbols sense, it is the heritage of humanity “. This must be read in correlation with the recognition of the fundamental role played by scientific research in our society, referred to in art. 12 of the same document: “Freedom of research”, which is necessary for the progress of knowledge and part of freedom of thought. 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 to a whole “. However, it is evident that the pursuit of research purposes can in no case prevail over human rights, fundamental freedoms and the dignity of the individual or groups of subjects (art.6).

More specific to the topic is the Recommendation on Human Biobanks and Genetic Research Databases (HBGRD) written by the Organization for Economic Co-operation and Development (OECD) which proposes to provide principles for the creation, governance, management, activities, access, use and possible interruption of biobank services and genetic databases for research purposes (Ducato et al, 2010).

Another important document that concentrates on the technical organization of the Biobank is the Best Practice Guidelines for BRCs (Biological Research Centres) written by OECD in which rules are supplied for the harvesting, the storage and the supply from the biological materials, and it creates qualitative standards for the BRC.

(This document was preceded by the Guidance for the Operation of Biological Research Centres (BRCs).

However, the most of these documents are regarded as soft law, it is necessary, therefore, to keep in mind their nature and consider their effective binding. In fact, these international instruments can only act as a model for national and EU legislation by providing guidelines and best practices developed because of a process of interaction with scientific institutions.

At the European level in fact is possible to detect a strong need to create shared taxonomies and provide a consistent framework capable of responding to the most pressing legal and ethical challenges raised by biobanks (Garcıa-Merino et al, 2011).

5. OVIEDO CONVENTION

The collection of biological material from humans is characterized by its gratuitous and voluntary nature, as established respectively in articles 21 and 10 of the Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine of 1997, better known as the « Oviedo Convention ». This is an international instrument and is binding for the countries which sign it, as it is the case with Spain (Vivas-Tesón et al 2013).

The Oviedo Convention, as a matter of fact, is the only international legally binding instrument on the protection of human rights in the biomedical field. It draws on the principles established by the European Convention on Human Rights, in the field of biology and medicine. The treaty entered into force only on 01/12/1999 after 5 ratifications by member states.

The aim of this document is to protect the dignity and identity of all human beings and guarantee everyone, without discrimination, respect for their integrity and other rights and fundamental freedoms about the application of biology and medicine.

Furthermore, the Convention is concerned with preserving the integrity, rights, fundamental freedoms, dignity and identity of the human being regarding the applications of biology and of medicine, by requiring signatory states to take the necessary measures to make the provisions of the Convention effective in their domestic law (art 1).

To achieve these objectives, it is essential to create an informed consent after providing the biological sample donor with clear and detailed information. In fact art. 22 of the Convention states that when a part of the human body is withdrawn because of surgery, it cannot be stored and used for purposes other than those for which consent was given. This means that the tissue stored in the biobank cannot be used for research if the patient has not signed the consent after being appropriately informed.

The Oviedo Convention, which is 21 years old, is now supplemented by 4 protocols: on the prohibition of human cloning, on human organ and tissue transplantation, biomedical research, and genetic tests for health purposes (Piciocchi, 2001).

However, is important to note that some relevant CoE States have still not signed it (such as Germany, Belgium, Austria, the United Kingdom or Russia) while others that have signed it have still not ratified it (Italy, Holland, Norway, or Poland).

Finally, although there are countries that still use unclear internal laws, there are others with well-organized legal framework.

6. RECOMMENDATION R (2016) 6

In addition to the Convention that has been analysed, the Council of Europe, recently, has specifically addressed the issues related to the collection and storage of biological samples in the Recommendation R (2016) 6 by the Committee of Ministers directed to the member States on research on biological materials of human origin.

This Recommendation regulates the medical-scientific research activity carried out through biological material of human origin removed and stored either for a specific research project and for different purposes (but still useful for research activities). Moreover, it recognizes the value of biomedical research for the advancement of health-care and for the improvement of quality of life and the potential of collection of biological materials of human origin.

It stresses the fact that research is often trans-disciplinary and international, as reflected in the establishment of international research infrastructures that pool and share samples and data across national borders.

Furthermore, it should be noted that the document in question also provides the right to withdraw or change the purpose for which consent was given (art 13). The exercise of this right can take place at any time and cannot cause to the subject any form of discrimination or prejudice, in particular regarding the right to health care (art. 10).

In this document, perhaps the most discussed part is article 10.2, which states that the use of samples requires appropriate informed consent in which the donor is aware of the research projects in which the sample will be used, in the manner as detailed as possible. However, a similar prediction raises some questions due to its formulation: it appears, in fact, difficult to do so.

Actually, it is particularly complex to illustrate at the time of sampling the possible future uses, especially in the long term.

7. LEGISLATION OF THE BIOBANKS IN SPAIN

In Spain, the transposition of the main international bioethics codes applicable to research with biological samples of human origin, as well as of the Committee of Ministers of the Council of Europe on research on biological materials of human origin, were implemented by the enactment of Act No 14/2007 on biomedical research and Royal Decree 1716/2011,13 establishing and regulating the authorization and functioning of biobanks for biomedical research. These are defined as public or private nonprofit establishments that store one or more collections of biological samples of human origin for biomedical research, organized as a technical unit with criteria of quality, order and purpose, regardless of storing samples for other purposes. Biobanks coexist with collections of biological samples of human origin created for biomedical research and stored outside the organizational scope of a biobank (Sospedra et al, 2016).

Spain has been one of the pioneers in this field because unlike other countries in which the regulation has been originated from the need to create biobanks to support large-scale projects, Spain has had, as a priority, to regulate the handling of already existing large collections of biological samples scattered through the network of the National Health Service hospitals, public research institutions, and universities. Because of that, the Biobank legal entity was created.

Despite this, the discussion on these topics in Spain is quite recent, in fact the Biomedical Research Act (BRA) was released in July 2007, in an attempt to respond to some previously identified shortfalls. The BRA has found a further development in the 1716/2011 Royal Decree that has come into force on June 2012. The Royal Decree defines the basic requirements for authorization and operation of Biobanks for biomedical research and also creates a National Registry of Biobanks. It embraces the different disciplines devoted to the study of human health and excludes others such as forensic investigation regulated in Organic Law 10/2007, of 8 October, regulator of the police database on identifiers obtained from the beginning of the DNA, and articles 326, 363 and additional provision third of the Law of prosecution criminal (Arias-Diaz et al,2013).

Moreover, this law allows the existence not only of biobanks as unique entities, but the possibility of creating a network of biobanks within the autonomous communities, authorized at national level.

Currently the Spanish regulation foresees three possible ways in which the samples for the research will be managed:

- Collection for use in a specific project
- Conservation in a collection
- Storage in a Biobank

The samples collected for a project are limited in time, having to be destroyed at the end of that particular project. For long-term storage of samples frame of a particular research line, there is a specific legal entity herewith termed 'collection.' A 'collection' is defined as "an orderly and permanent set of human biological samples that are stored outside the Biobank regime". These samples cannot be transferred to third parties or used for other research projects, nor transferred to other facilities outside the patient's informed consent.

The regime applicable to Biobanks is different from that of collections, because the primary objective of Biobanks is to serve as platforms to provide the scientific community with high-quality samples. This means that all the samples obtained from medical or diagnostic operations, to be included in the biobanks must comply with the rules of BRA, and therefore implies that most departments of pathological anatomy should have a biobank inside them or be associated with an external one.

Another interesting feature of the Spanish legislation for the regulation of biobanks is the creation of a National Register, of which the The Carlos III Institute of Health is entitled for the maintenance, available at the public level.

Moreover, an important aspect regarding the Spanish regulation is that it confers a well-defined structure to biobanks to guarantee high standards both in terms of quality and in terms of legal and ethical administration.

Accordingly, a Biobank should have at least:

- a title holder (person or an institution)
- a management structure made up by a Scientific Director, a person responsible for the personal data file two committees of external experts, a scientist one and an ethical one.

To qualify as an 'external committee' none of the members can be part of the structure of the Biobank or have any conflict of interest with the activity of the same institution. The essential role of both committees will be to report on the ethical and scientific aspects of the incorporation of existing sample collections to the Biobank and to report on the transfer of samples to other Biobanks or research groups. The biobank can be ascribed to the CEI (Comité de Ética de la Investigación) of the center to act as its external ethics committee, but only in case none of its members forms part of the structure of the biobank (Best Practices oecd.org).

About the characteristics of the scientific committee, the current regulations do not specify anything about it, so it is clear that there should be people with sufficient knowledge to evaluate research projects from a scientific point of view, and who do not belong to the biobank and are free from conflict of interests with it.

But, if these considerations have been used to trace the general scenery of the current regulation of biobanks at the state level, we cannot ignore the activity that has been developed in the area of the autonomous community in the hands of the corresponding assumption of competences, and its normative development (www.redbiobancos.es).

One of the first biobanks in the autonomous society of Madrid is located in the CNIO (Centro Nacional de Investigaciones Oncológicas) until 2002.

CNIO Biobank forms part of the National Biobank Network, promoted by the Carlos III Health Institute (ISCIII) and it was the first institute to coordinate this network from 2010 to 2017 taking the key role as coordinator of the whole network in which 39 institutions participate as a guide and a source of information for the development and planning of social welfare policies and for research.

8. LEGISLATION OF THE BIOBANKS IN ITALY

In Italy the situation regarding the legal and structural organization of biobanks appears to be more complicated. In fact, a legal definition of "biobank" does not exist in the Italian regulatory system. In this regard, the first non-binding document that offers the main definition of "genetic biobank" was issued in 2003 by the Italian Society of Human Genetics.

The ethical-legal framework of research biobanking activities is still scarcely defined, and this constitutes a major obstacle to exploit the potential benefits of existing bioresource patrimony at the national and international levels. This fragmentation creates uncertainty, which in some cases hampers medical research (Calzolari et al 2013, Piciocchi et al 2018).

On the other hand, in Italy, there is a well-defined ethical and legal framework for therapeutic biobanks for the collection of tissues, blood, and cells, and for any therapeutically use of biological samples:

- Legislative Decree 6 November 2007, No. 191, implementing Directive 2004/23/EC on setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells.

- Legislative Decree 19 August 2005, No. 191, implementing Directive 2002/98/EC setting standards of quality and safety for the collection, testing, processing, storage and distribution of human blood and blood components, as modified by Legislative Decree 20 December 2007, No. 261 and Law 1 April 1999, No. 91, about organs and tissues transplantation.

However, conversely, there are no specific provisions applicable to biobanks for scientific research, and the legal and regulatory frameworks regarding the use of bio-samples and related data are fragmented, with variation of practice across different areas of medical research. These activities are currently subject to rules mainly derived from guidelines and "soft laws" instruments, such as nonbinding recommendations issued by ethics committees and scientific associations. Indeed, many areas of biobanking, such as the definition and functioning of research biobanks and the matter of signed informed consent, are mainly addressed by scientific experts' guidelines which are not legally binding but are very useful tools as they try to create a regulatory framework to guide research and to increase confidence about the ethical principles and the rights of participants in biobanking-based research. On the other hand, patenting and data protection are regulated by binding directives.

The processing of genetic data for example in Italy is governed by a regulation that is, in many respects, stricter than those existing in other EU Countries.

All these organizational and legislative differences make it difficult to exchange data and samples therefore also the scientific research itself (Ducato 2013).

This situation will most likely change, with the entry into force of the new General Data Protection Regulation (GDPR). This act, approved in May 2016, will repeal Directive 95/46/EC with effect from 25 May 2018: this two-year period will allow Member States to revise or adapt their legislation in order to comply with the GDPR. This shift in paradigm from a Directive (setting certain aims to be achieved) to a Regulation (setting specific rules to be complied with) can be referred to as a 'harmonization through adaptation' process (Van Ommen et al 2015).

From the general viewpoint of the scope of the Regulation, with regard to the functioning of biobanks, Art. 4 (3b) introduces a definition of "pseudoanonymisation", which is defined as "the processing of personal data in such a manner that the personal data can no longer be attributed to a specific data subject without the use of additional information, provided that such additional information is kept separately and is subject to technical and organizational measures to ensure that the personal data are not attributed to an identified or identifiable natural person" Article 4 (5).

1. Despite of this, Italy is also currently a part of the recently established pan-European Biobanking and BioMolecular resources Research Infrastructure - European Research Infrastructure Consortium (BBMRI-ERIC) that aims to improve accessibility and interoperability between academic and industrial. BBMRI-ERIC is developing the concept of the Expert Center as public-private partnerships in the precompetitive, not-for-profit field to provide a new structure to perform research projects (21).

9. CONCLUSION

The biobanks are precisely a large collection of biological or medical data and tissue samples, amassed for research purposes, that organized the sorting and the storage in a structured way of the biological materials and the related complete clinical data, giving guarantees of traceability and quality never reached in the history of research.

The studies and research in the field of oncology and for the other complex diseases have clearly demonstrated that the opportunity and the need to have a series of samples of biological materials, conserved and correlated with complete clinical pathological data, has become increasingly pressing. This need, deriving from the transformation of medicine from an art to a science, can be simply solved with the tools that science gave itself for the same objective, namely the development and integration of extensive databases, correlable and structurally integrable: the biobanks.

Obviously, the development of biobanks is not at no cost, and brings with it problems. Not so much technological, namely the availability of huge databases that are fast, expandable and interconnectable, with high quality guarantees; but rather legal and ethical, in the sense that all this information must be collected and dealt in accordance with the national and international rules and laws that concern the protection of citizens' privacy and their right to self-determination.

In this paper are discussed the problems related to the development of biobanks related to two nations, Italy and Spain, but the same ethical and legal issues are extended to the whole world, and on these the comparison is very open.

This situation leads to two negative consequences, which aggravate each other:

- on the one hand the researcher goes in search of alternative possibility to the use of biobanks to find big numbers of samples

- on the other hand, these samples, not being guaranteed, controlled and standardized, can affect the correctness of the results of the research

For the reasons mentioned above, it is clear that the availability of large bio-medical banks is essential to promote medical research, especially in those sectors where statistics made on large numbers are essential to decrease the margin of error of the results.

In our opinion, there are two tools that can really incentivize the creation and use of bio-banks:

- to ensure that journals, who publish scientific works, ask for the origin of the samples used as the prerequisite for publication, thus encouraging the mechanism for using bio-banks.

- to optimize the management of funds allocated to existing biobanks, so that they should not only

used to improve their operation, but also to promote the search for further donations from other private associations, such as pharmaceutical and computer industries, to increase the number and structure of biobanks.

- to promote, from a legal, legislative and ethical point of view, an information and lobbying activity aimed at building management standards of clear, targeted and usable bio-medical data at a global level.

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