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EDITORIAL ARTICLE

Biomedical research with human biological samples: A new challenge for Bioethics and for the Clinical Research Ethics Committees☆

Investigación biomédica con muestras biológicas de origen humano: un nuevo reto para la Bioética y los Comités Éticos de Investigación Clínica

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Ideally, all scientific advances should result in a better quality of life for society, reducing inequalities between individuals. This thinking is in line with the latest revision of the Declaration of Helsinki (Fortaleza, 2013),[1] which significantly affects the social dimension of biomedical research, clearly influenced by the bioethical principle of justice reflected in the Belmont Report (1978).[2] The article by Alfonso Farnós et al. in this issue of the ''Revista Española de Medicina Legal'' [''Spanish Journal of Legal Medicine''] rightly addresses an aspect discussed in the field of clinical trials: the use of biological samples and the methodological, ethical, and legal implications.[3]

Genetics and related sciences have seen continuous growth since Oswald T. Avery and Maclyn McCarty showed that genes are composed of deoxyribonucleic acid molecules in the mid-twentieth century.[4] Since then, new knowledge and applications have been established, such as genetic engineering and ambitious research projects like the *Human Genome Project*[5] or the ENCyclopedia of DNA Elements (ENCODE) Project.[6] In legal and forensic medicine, we cannot ignore the discovery in 1984 of so-called genetic fingerprinting by Alec Jeffreys.[7] The speed with which these events are happening far exceeds the capacity of society to assimilate this knowledge.

The possibility of obtaining information on the genetic endowment of an individual and even the ability to manipulate it—gene therapy—is a new paradigm in medicine, with the advent of so-called personalised medicine. The potential applications of this immense knowledge on prevention, diagnosis, and treatment of genetic diseases is one of the main fields of academic and hospital study, not to mention the enormous interest that this area of knowledge entails in research into new therapeutic targets and biologic drugs

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that are much more selective and safer than traditional drugs, developed mainly by the pharmaceutical and biotechnology industries.

Despite the many advantages for medicine emerging from advances in genetics and biotechnology, we should not ignore the potential risks associated with their misuse. Misuse or illegal use of an individual's genetic information by unauthorised third parties can result in what is known as ''genetic discrimination'', a form of violation of the right to privacy which can have significant consequences, not only for the individuals themselves but for their direct descendants and family members, due to the marked interpersonal nature of genetic information. In fact, in the US, the Genetic Information Nondiscrimination Act (GINA) was enacted to protect individuals from misuse of genetic information by health insurance companies and human resource companies.[8]

Bioethics emerged in the US in the mid-1970s, in response to the social alarm rung by various cases of flagrant violation of fundamental human rights in the name of scientific progress. Van Rensselaer Potter, an American biochemist considered the father of bioethics, understood this new discipline to be a bridge between the humanities and the hard sciences, integrating biology, medicine, ecology, and human values. This period saw the creation of the first bioethics institutes and *Institutional Review Boards*, which in our setting are called Independent Ethics Committees, as fora for the discussion and evaluation of major bioethical dilemmas encountered in biomedical research, the main objective of which is to ensure the safety and welfare of human beings taking part in biomedical research projects. The Declaration of Helsinki, in its Tokyo version (1975), first took into account the need for formal review of the research protocol by an independent ethics committee.

The basic principles of bioethics (respect for the person or autonomy, beneficence/non-maleficence, and justice), the result of serious consideration by the *National Commission for the Protection of Human Subjects of Biomedical and Behavioural Research*, which was created by the US Congress in 1974, are the fundamental pillars on which bioethics deliberations are based.[9] Independent Ethics Committees have fully internalised the principles of bioethics in the evaluation of biomedical research projects involving direct participation of human subjects. Compliance with the principle of respect for the person or autonomy is guaranteed by assessing the informed consent procedure and the measures for protecting the confidentiality of data of project participants. Respect for the principles of beneficence and non-maleficence are mainly guaranteed by assessing the suitability of the research team, the scientific validity of the project, and the risk–benefit ratio for participants. Finally, respect for the principle of justice is guaranteed by assessing the project's eligibility criteria (inclusion and exclusion).

The traditional setting is changing gradually because a large part of biomedical research projects submitted to Independent Ethics Committees are genetic studies that involve the sole and exclusive use of biological samples associated or not with clinical data on the source subjects (i.e. the origin of the biological samples). Clinical research, which is based on analysis of a direct or indirect intervention (observational studies) on human beings, is being displaced by research based on the use of biological samples of human origin, whose implications and consequences go beyond the limits set by the scientific protocol itself, and in which the assessment of the risk–benefit ratio is at times difficult to establish.

At this point, the principlist focus of bioethics became insufficient to provide security to the scientific community, guaranteeing the right to research as well as respecting fundamental human rights and dignity. It therefore became necessary to have a specific ethical and legal framework of reference for this promising knowledge area.

The main international bioethics codes emerged at the end of the 20th century, including the Oviedo Convention[10] and the Universal Declaration on the Human Genome and Human Rights of UNESCO,[11] as reflected in the extremely important aspects laid down in their provisions, such as the prohibition of all forms of discrimination of a person's genetic heritage, or the conduct of predictive analysis of genetic diseases solely for health reasons or related scientific research, among others.

In Spain, the transposition of the main international bioethics codes applicable to research with biological samples of human origin, as well as Recommendation Rec(2006)4 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[12] and Royal Decree 1716/2011,[13] establishing and regulating the authorisation and functioning of biobanks for biomedical research. These are defined as public or private non-profit establishments that store one or more collections of biological samples of human origin for biomedical research, organised 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 organisational scope of a biobank. According to current legislation, biobanks and collections of biological samples of human origin created for biomedical research should register in the appropriate section of the National Registry of Biobanks of the Instituto de Salud Carlos III. Strict compliance with this mandate is shown in the case of accredited biobanks. In the case of collections, however, a registry search suggests that there are still many undeclared collections. Biobank personnel and Independent Ethics Committees are tasked with informing, educating, and persuading biomedical investigators of the desirability of registering their ''private'' collections in the Registry to comply with existing legislation. But most importantly, this an exercise of the investigators' responsibility and good scientific practice in all matters relating to the management of these collections.

Quality biomedical research from a scientific point of view implies, increasingly in our globalised world, collaborative work between several teams, institutions, and research sites. Article 33 of Royal Decree 1716/2011 establishes the obligation to sign an agreement of assignment or transfer of samples *(Material Transfer Agreement)*, within the framework of a research project, between the person responsible for the collection of origin, stored within or

outside a biobank, and the person responsible for the target biobank or private collection. In short, this agreement should cover all aspects related to the traceability of the samples, including the final destination of surplus samples of the project to which they were assigned, and the return of all validated genetic information that may be relevant to the source subject. Recently, Royal Decree 1090/2015,[14] regulating clinical trials with medicinal products, which came into effect on 13 January 2016, also contemplates the implementation of Royal Decree 1716/2011 in the case of surplus biological samples of a clinical trial or those collected during the trial expressly for future research. In this case, the preparation and management of the *Material Transfer Agreement* is a sensitive matter, because most of the biological samples generated in the clinical trial context will be stored in private collections managed by pharmaceutical or biotechnology multinationals located outside Spain, perhaps even outside the European Union, which are naturally not registered in the National Registry of Biobanks.

Biobanks, private collections of biological samples, and material transfer agreements have become common expressions and objects of discussion in Independent Ethics Committees. Article 2(e) of Act No 14/2007 on biomedical research, establishes the requirement that all research projects involving the use of biological samples of human origin be previously assessed and approved by an Independent Ethics Committee. In practice, the assessment of such projects has been assumed in many cases by Independent Ethics Committees for Clinical Research, which have extensive experience in assessing the methodological, ethical, and legal aspects of clinical trials of medicinal products and medical devices, postmarketing observational studies of medicinal products, and other observational studies, although they are less used to assessing this type of research projects. To respond to the new legal requirements, Committees have incorporated specialists in various areas of knowledge related to genetics, biotechnology, and related sciences.

The current Spanish legislation, inspired by international bioethics codes and recommendations, has undoubtedly provided legal safety to all stakeholders involved in biomedical research with biological samples of human origin. However, certain important practical aspects have yet to be resolved. These affect, among others, the Independent Ethics Committees themselves, especially in relation to the lack of uniformity in the criteria for assessing research projects which, to some extent, led to the failure of the so-called ''single opinion'' established by Royal Decree 223/2004[15] of 6 February, regulating clinical trials of medicinal products. This lack of consensus has worsened in terms of assessing research projects involving the use of biological samples of human origin, within the framework of the functions entrusted by Act No 14/2007 on biomedical research. This has resulted in a more or less strict application of the precautionary principle, which has often led to misunderstandings among Independent Ethics Committees themselves, and between them and the scientific community at large.

It is therefore imperative to adopt a common position among all accredited Spanish Independent Ethics Committees, which guarantees that biomedical research has a high degree of scientific, ethical, and legal quality, while respecting fundamental human rights and dignity.

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