Review of the Italian Current Legislation on Research Biobanking Activities on the Eve of the Participation of National Biobanks' Network in the Legal Consortium BBMRI-ERIC

Alessia Calzolari,* Mariarosaria Napolitano,* and Elena Bravo

The ethical-legal framework of research biobanking activities is still scarcely defined in Italy, and this constitutes a major obstacle to exploit the potential benefits of existing bioresource patrimony at the national and international levels.

Biobanking and Biomolecular Resources Research Infrastructure (BBMRI), which aims to become a major interface between biological samples and data and top-level biological and medical research, is undertaking the crucial transformation to the ERIC (European Research Infrastructure Consortium) legal entity. In this scenario, there is a need to address the national legal and ethical concerns that are strictly correlated with the use of human biosources in research across European countries participating (and not) in BBMRI. In this perspective, this article aims to review the legal framework applying to research biobanking in Italy, including both "soft" nonbinding instruments and binding regulations. Since ethical and societal aspects impact biobanking research activities, the article discusses both the critical ethical and legal open issues that need to be implemented at the national level.

Introduction

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 therapeutical use of biological samples.^{1,2} 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. This fragmentation creates uncertainty, which in some cases hampers medical research.

The aim of this article is to give an overview of this complexity, by discussing the main legal requirements for biobanks at the Italian level, to provide a brief outline of the regulatory bodies that are responsible for ensuring best practice for biobanking activities and to discuss some ethical and legal issues that need to be implemented at the national level. Since Italy has shown a great interest in joining the European Research Infrastructure Consortium (ERIC)³ of Biobanking and Biomolecular Resources Research Infrastructure (BBMRI), reviewing the national legislation that covers biobanking would be of interest for Italian stakeholders

of biobanking initiatives. BBMRI (www.bbmri.eu) is the forthcoming pan-European research infrastructure on biobanking that is built on existing infrastructures, bioresources, and technologies, specifically complemented with innovative components and properly embedded into European ethical, legal, and societal frameworks. Thus, there is a need to address many legal and ethical concerns that are strictly correlated with the use of human biosources in research across European countries participating (and not) in BBMRI. On the other hand, taking into account that effective collaboration among European countries is becoming increasingly important, the Italian situation could serve as a useful comparison for the European scientific community dealing with different national regulations. Thus, the reciprocal knowledge of the different regulations across European countries becomes a suitable tool to accelerate the process of integration and interoperability in European and international biobanking.

Italian Biobank Regulation

A gap exists between the creation and operation of biobanks in Italy and the legal framework needed to regulate them. These activities are currently subject to rules mainly

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Department of Hematology, Oncology and Molecular Medicine, Istituto Superiore di Sanità, Rome, Italy.

*These authors contributed equally to this work.

TABLE 1. NATIONAL LAWS AND GUIDELINES THAT IMPACT ON ITALIAN RESEARCH BIOBANKING

<i>Law/guideline</i>	<i>Status</i>	<i>Covered issues</i>
Legislative Decree 6 November 2007, No. 191	Binding/"hard" law	General frame for Quality and safety of human tissues and cells
"Guidelines on Genetic Biobanks", Italian Society of Human Genetics, 2004	Nonbinding/"soft" law	Definition of genetic biobanks
"Guidelines for the institution and the certification of biobanks", National Committee for Biosecurity and Biotechnology, 2006	Nonbinding/"soft" law	Definition of genetic biobanks
Permanent Conference for Relations between State, Regions and Autonomous Provinces of Trento and Bolzano, Rep. Acts no. 57/CSR of 25 March 2009	Nonbinding/"soft" law	Definition of biobanks
Permanent Conference for Relations between State, Regions and Autonomous Provinces of Trento and Bolzano, Rep. Acts No. 21/CSR of 10 February 2011	Nonbinding/"soft" law	Definition of biobanks
Collection of biological samples for research: informed consent. National Bioethics Committee and National Committee for Biosafety, Biotechnologies and Life Sciences, 2009	Nonbinding/"soft" law	Informed consent
Legislative Decree 13 August 2010, No. 131	Binding/"hard" law	Patenting and industrial property
Legislative Decree 30 June 2003, No. 196	Binding/"hard" law	Privacy and data protection
General authorization for the processing of genetic data, 24 June 2011	Binding/"hard" law	Privacy and data protection
General authorization to process personal data for scientific purpose, 1 March 2012	Binding/"hard" law	Privacy and data protection

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 (Table 1), 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 (Table 1).

A schema of the Italian regulations which impact on research biobanking is reported in Table 1.

Definition of "Research Biobank"

A legal definition of "biobank" does not exist in the Italian regulatory system. In this regard, the first nonbinding document that offers the main definition of "genetic biobank" was issued in 2003 by the Italian Society of Human Genetics.⁴ According to these Guidelines, "genetic biobanks" are defined as "nonprofit service units created for the collection and storage of human biological material used for genetic diagnosis, the study of biodiversity, and for research." This document also specifies that the stored samples must "be linkable to the personal, genealogical, and clinical data of the subjects from whom the deposited material has been collected."

Another definition of "biobank" was provided in 2006 by the National Committee for Biosafety, Biotechnology, and Life Sciences (NCBBLs) with the "Guidelines for the Institution and Certification of Biobanks,"⁵ which define "genetic biobanks" as collections of human samples that can be linked to the anagraphic, genealogic, and medical data of the persons from which they have been extracted."

In 2009, an act of the forum "Permanent Conference for Relations between State, Regions and Autonomous Provinces of Trento and Bolzano,"⁶ defined "biobanks" as "service units, located within nonprofit public or private health facilities, for the collection, processing, preservation, storage, and distribution of human biological material, for diagnostic purpose, research and therapeutic use" (Rep. Acts no. 57/CSR of 25 March 2009).⁶

The same forum addressed the matter of biobanking a second time with the "Technical Document of Guidance to Reduce the Burden of Illness of Cancer"⁷ (Rep. Acts No. 21/CSR of 10 February 2011), in which a biobank is defined as "a collection of biological samples and associated clinical data." Furthermore, the document states that each biobank must provide for the collection, storage, and distribution of biological samples, and that the decision on the type of tissue to be stored belongs to individual biobanks, based on the different clinical and research needs. The document emphasizes the absence of a legislative framework governing the establishment and management of biobanks, highlighting that, in the absence of a specific national regulatory framework, the recommendation of the Council of Europe on the use of human biological materials⁸ is the only organic document that rules the use of human biological materials.

Signed Informed Consent

The governance framework for medical research is based on the fundamental principle that individual research participants must be respected. This is demonstrated through the requirement that consent must be obtained from research participants before the research commences and this should be informed and voluntary.

One of the most important problems for people working in the sector of medical research with biological material is to establish when and how it is legal to preserve samples beyond the time necessary to achieve the aim for which the sample

was collected, and if it is also legitimate to use samples for purposes that are different from those initially identified. Tissues collected for diagnostic purposes must be kept by hospitals for at least 20 years. However, despite the widespread practice of scientific research institutes of storing collections for future studies beyond the primary research scope, no specific regulation deals with biosample storage time.

In the absence of specific rules and to try to limit the heterogeneity of consent forms accepted by dozens of ethical committees in charge in the country, the so-called Joint Group comprised of members of the National Bioethics Committee (NBC) and the NCBLS developed a specific guideline⁹ in order to contribute to the harmonization process of the signed informed consent used by Italian research biobanks. This guideline emphasizes that the donation of biological material has many moral values: it is an act that can benefit other people, immediately or in the future, and it is an act of prudence in the case of their future needs. For these reasons, the donation is always to be considered as a free and informed act, from which one can withdraw.

The signature of the proposed informed consent form allows people to express an attitude of solidarity by donating their biological samples. This consent form tries to balance the public interest and the need for the respect of individuals' values and fundamental rights, in agreement with Article 2 of Oviedo Convention,¹⁰ which states: "The interest and benefit of man must prevail on the mere interest of society and science."

Many studies on informed consent forms highlight that people generally want to control whether their samples are used for research purposes, but also that the majority of them is happy to donate samples.^{11,12} The model of signed informed consent elaborated by the NBC and the NCBLS respects this request, by informing donors about the future use of the biological material and the information derived from it, as well as by guaranteeing that the correct procedures are adopted in order to protect personal data. The ambiguity in the use of the concept of "anonymizing" the samples is also addressed by the guideline.

Industrial Property and Patenting Issues

One of the critical points of Italian legislation is represented by patent development based on bioresources' use. With Legislative Decree No. 131 of 13 August 2010,¹³ which amended a number of provisions of the Code of Industrial Property,¹⁴ the Italian Government introduces restrictive measures pertaining to the use of biological material for biotechnological inventions. In particular, Article 87 of the aforementioned Decree states that "The demand for patent relating to an invention which has the purpose or uses biological material of human origin must be accompanied by the free and signed informed consent, to such collection and use, of the person from whom such material was taken, in accordance with current legislation." The legislation also introduces in Article 88 severe pecuniary sanctions for the use of biological material for the purpose of patenting an invention, without the signed informed consent of the interested persons.

Privacy and Data Protection: Provisions of the Italian Data Protection Authority

Since the functioning of a biobank normally implies the processing of personal data, especially medical and genetic

data, the protection of privacy is among the most sensitive issues in biobanking. This matter is specifically addressed by laws issued by the Italian Data Protection Authority, who is responsible for the processing of personal data belonging to high-risk categories. First of all, any biobank activity must comply with the provisions of the Data Protection Code (Legislative Decree no. 196 of 30 June 2003),¹⁵ in particular with those concerning access to and communication of personal medical and genetic data. To fully regulate this delicate topic, the Italian Data Protection Authority issued a "General authorization for the processing of genetic data."¹⁶ This provision establishes that genetic data may be processed exclusively for specific purposes, and only with the consent of the data subject. Furthermore, the processing of genetic data must be indispensable, that is, the same purpose cannot be achieved through the use of anonymous genetic data or other kinds of personal information. In addition, it is possible to make further use of biosamples and genetic data if research for similar purposes cannot be performed by processing data relating to individuals that can or have been able to provide their new informed consent.

The more recent Resolution No. 85 of 1 March 2012 of the Italian Data Protection Authority on "General authorization to process personal data for scientific purpose,"¹⁷ which allows the use of "data of the interested parties to be included in research if they cannot be contacted," deals with the use of samples collected by people who cannot be contacted, and the exchange of samples between research groups. The general authorization simplifies the legal procedures concerning scientific studies based on the secondary use of personal data. The new authorization is related to "the processing of personal data suitable for disclosing data subjects' health, also without their informed consent" for retrospective observational studies, when they cannot be informed because of particular reasons and the research program obtained the competent Ethics Committee's favorable opinion. Exemption for collecting a new signed informed consent for health research using data or samples already collected include: (i) "ethical grounds," that "have to do with the fact that the data subject is unaware of the respective health condition; this applies to any research if providing information to data subjects on processing of their data entails the disclosure of information on the specific study being carried out, which information might cause tangible or mental harm to the said data subjects;" (ii) "organizational grounds", that "have to do with the fact that the failure to include the data relating to the estimated number of data subjects that cannot be contacted in order to be informed [omissis] would impact significantly on the study by altering the relevant findings" and apply when the subjects, "following all reasonable efforts made to contact them," cannot be contacted in order to be informed.

In these situations, Resolution No. 85 of 2012 allows "universities, other research bodies or institutions, and scientific societies" to use the personal data already collected, even without the consent of the person in question, thus facilitating biomedical research in the total respect of patients' rights concerning data protection and privacy. A new signed informed consent is clearly necessary when patient contact information is available. The authorization also deals with procedures regarding personal data management, including safety treatment, storage, and transfer abroad of data and samples, and dissemination of research findings. It

is important to note that the authorization does not apply to genetic data, for which special authorization is required,¹⁶ but to the re-use of personal data already collected.

With respect to the previous laws, the deliberation issued in 2012 marks a more flexible approach as regards the protection of personal data^{18,19} in some specific cases. For instance, this provision has a relevant impact on the use of archival fixed and paraffin-embedded (FPE) tissues. Italy has a long tradition and rich archives of pathologic residual diagnostic and surgery clinical material stored as FPE samples in hospitals and pathology departments. FPE archives are the most abundant source of annotated human tissues and also representative of clinical heterogeneity, and their use may strongly contribute to advancement of cancer research. However, for most of these tissues, the consent for research use is not available. The significance of most of these samples derives from being collected for diagnostic purposes and directly related to the health of patients.²⁰

Furthermore, re-contacting the patients in order to obtain a consent for the research is organizationally complex, expensive, and, in most cases, unsuccessful (patients are dead or not contactable). As most of these situations are within the "organizational reasons," the deliberation of 1 March 2012 will facilitate the use of large FPE archives and will improve the availability of histologically classified human tissues for translational research and validation and standardization of diagnostic, prognostic, and therapy predictive biomarkers.

Open Issues and Conclusions

In order to guarantee the rights of the donors, as well as to ease the task of the researchers, the Italian Legislature needs to consider various unresolved issues in the field of biobanking. A systematic regulatory framework for biobanking is needed to resolve most of the uncertainty burdening health care research and to provide security and quality for stored human biological samples and correlated medical and genetic data through the establishment of ethical and operational standards shared at an international level.

First of all, the lack of a legal definition of the entity "biobank for research purposes" does not allow the discrimination between "biobanks" and "collections of biological samples." Legislation on biobank infrastructure requirements and management, as well as data storage and access policy for biobanks' research use, is very incomplete. As an effect of the recently introduced devolution in the Italian health system, which has decentralized health services from the central government to the regional level, the Regions are the territorial authorities appointed to define the criteria for biobanks' accreditation and to recognize those biobanks that fulfill the quality requirements. To avoid significant heterogeneity in accreditation criteria among the 21 Italian Regions and the 2 autonomous Provinces in charge of the accreditation procedure, an "Inter-regional forum (Tavolo inter-regionale sulle biobanche)" is working on the harmonization of the recognition criteria. The recent renewed expression of interest by the Italian Ministry of Health to participate in BBMR-ERIC is strongly accelerating the process of finalizing the organization of the national Node and recognition of biobanking criteria represents an important step towards the final organization of the Italian Node of BBMRI. According to the present calendar of the activities (updates available at www.bbmr-eric.i), it is foreseen that the implemented structure of the Italian national

node will be presented to the scientific community at the next European, Middle Eastern, and African Society for Biopreservation and Biobanking (ESBB) annual meeting, which will be held in Verona (October 9–11, 2013).

"Certification" of research biobanks by an independent organization appointed to evaluate, certify, and monitor the presence of internationally recognized requirements^{21,22} is a parallel process that needs to be developed soon both at national and international levels.

It is noteworthy that the Italian situation reflects the challenges of biobanking governance within Europe. The issue of the fragmentation of biobanking practices and activities across European countries has been recently addressed in a report published in 2012 by the European Commission.²³ In this report, an interdisciplinary group of experts deals with the ethical and regulatory challenges of international biobanking and strongly recommends Member States to "develop a consistent and coherent legal framework for biobanking" in order to "protect participants' fundamental rights, in particular in the areas of privacy, data protection and the use of human tissue in research."

Concerning data protection, in 2012 the European Commission published a proposal for a new Regulation²⁴ to replace Data Protection Directive 95/46/EC.²⁵ The aim of this revision is to protect the fundamental rights and freedoms of persons, while ensuring the free flow of data within the EU, in order to respond better to challenges posed by the rapid development of new technologies and increasing globalization. To overcome the current fragmentation across the EU Member States, the proposed provision allows the adoption of a single set of rules on data protection, valid across the EU. This will foster better cooperation between national data protection authorities and will remove unnecessary administrative formalities, such as general notification requirements, leading to saving related economic costs for companies and businesses. The Commission's proposal, overall, tries to achieve the right balance between strengthening individual data protection rights and stimulating progress and innovation, especially concerning the processing of health data for scientific research. However, the practical impact on research biobanking activities and on the current Italian legislation is, as yet, unknown, since the proposal appears to be incomplete, with regard, for instance, to the use of personal data for a secondary research purpose. Following the on-going discussion and implementation, the practical impact on research biobanking will become clear and a common regulation will surely contribute to ameliorate the interoperability at the European and international level.

In conclusion, the building of an efficient international biobanking network must be supported by clear regulations, both at national and international level, which provide biobanks with standards for addressing ethical and legal challenges and ensures donor rights' protection.

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Address correspondence to:

Dr. Elena Bravo

Department of Hematology, Oncology and Molecular Medicine

Istituto Superiore di Sanità

Viale Regina Elena 299

00161, Rome

Italy

E-mail: elena.bravo@iss.it