Chapter 17
Biobanks for Biomedical Research: Evolution and Future

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Abstract For more than two decades, in the era of post-genomics and personalized precision medicine, biobanks for biomedical research have successfully fostered the development of basic and translational biomedical research. The expansion of biobanking has brought a wide and intense debate on ethical, legal and social implications (ELSI) when using large numbers of human biological samples and associated personal data. All these challenges are relatyed to the fact that these infrastructures allow several future research projects to be carried out along general lines of research, with the use of samples and sensitive information, such as genetic data, which can be shared internationally, and whose specific purpose the donor cannot know at the time of donation. In this chapter, I will address the challenges that have emerged at the different stages of the evolution of biobanks, from biobanks' governance stage to the sustainability stage, through the harmonization and collaboration networks stage, in order to address the challenges biobanks will deal with in the near future.

Keywords Biobanks · Governance · Sustainability · Ethics · Law

Introduction

Biobanks for biomedical research have been successfully promoting the development of basic and translational biomedical research for more than two decades, in the era of post-genomics and personalized precision medicine (Coppola et al., 2019). In 2009, *Time* magazine included biobanks among the "10 ideas that are changing the world right now". The International Agency for Research on Cancer noted in 2017 that biobanks are on the base of three rapidly expanding fields of

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biomedical science: "(i) molecular and genetic epidemiology (aimed at assessing the genetic and environmental basis of cancer causation in the general population as well as in families), (ii) molecular pathology (aimed at developing molecular-based classification and diagnostic procedures for cancers) and (iii) pharmacogenomics/pharmacoproteomics (aimed at understanding the correlation between an individual patient's genotype or phenotype and response to drug treatment) (Mendy et al., 2017).

However, the expansion of biobanking has also brought with an extensive and intense debate about Ethical, Legal and Social Implications (ELSI) of the use of large numbers of human biological samples and associated personal data, including genetic data, for people who have donated them, as well as for the community and society in general (Chadwick & Cutter, 2007).

In this chapter, I will review the change in biomedical research, from ethical and regulatory perspectives, which resulted from the use of biobanks as platforms for future use of biological samples and associated data for research purposes, available to be requested by any researchers in different research projects. We will analyze this process through three stages of the evolution of biobanks. First stage, which includes the ethical challenges to systematically manage the future use of samples in relation to informed consent for biobanking, the right to withdraw consent, secondary use of biological data and samples, privacy and confidentiality, international sample and data sharing, communication of results and disclosure of incidental findings. Second stage, corresponding to the challenges of regulatory harmonization and the creation of national and international biobank networks as a result of the necessity to share large quantities of quality samples to promote the development of research, by improving access and sustainability. Third stage, addressing the sustainability challenge of biobanks, particularities as compared to other biomedical research infrastructure and the dimensions in which this challenge has to be analyzed for a comprehensive understanding.

Concept and Classification of Biobanks

Since it appeared in scientific journals in the mid-1990s, the term "biobank" has had various definitions in reports, policies and guidelines from national and international organizations without coming to a clear and final consensus (Hewitt & Watson, 2013). However, over time, a broad definition based on three elements has begun to be accepted: (i) they are collections of human biological samples and associated personal data, (ii) organized with technical, ethical and regulatory standards, (iii) that can be used by any researchers in different future research (Vähäkangas et al., 2021). The Organization for Economic Cooperation and Development (OECD) (2010) defined a biobank in a broad sense, using the term "human biobanks and genetic research databases," understood as "structured resources that can be used for the purpose of genetic research and which include: (a) human biological materials and/or information generated from the analysis of the same; and (b) extensive associated information". Nevertheless, this definition does not refer to one of

the essential characteristics of biobanks, access to the sample by third parties and the way they are managed.

The European Commission, to provide further clarification on the scope of the term, in its *Biobanks for Europe Report. A Challenge for Governance* (2012), defines them as "collect biological samples and associated data for medical-scientific research and diagnostic purposes, and organize these in a systematic way for use by others". The report highlights this last aspect, since what distinguishes biobanks from a collection of samples is the existence of "governance mechanisms in place to allow access to the resource in a systematic way to outsiders." In this sense, the Commission decided to define biobanks based on a set of characteristics that describe their activity through governance that guarantees the rights of donors, transparency and public trust. The report highlights the following aspects: "(a) collect and store biological materials that are registered not only with medical, but often also epidemiological data (eg environmental exposures, lifestyle/occupational information); (b) are not static "projects", since biological materials and data are usually collected on a continuous or long-term basis; (c) are associated with current (defined) and/or future (not yet specified) research projects at the time of biospecimen collection; (d) apply coding or anonymization to assure donor privacy but have, under specific conditions, provisions that participants remain re-identifiable in order to provide clinically relevant information back to the donor; and (e) include established governance structures (e. g. ethics review committees) and procedures (e. g. consent) that serve to protect donors' rights and stakeholder interests" (European Commission, 2012, p. 13).

Biobanks may be classified according to their type, size, purposes, forms of access, controllers, among others. The wide heterogeneity of biobanks has raised, beyond a definition, "the need for a universally-accepted, systematic classification of the different biobank types" (Hewitt & Watson, 2013). One of the most common criteria for classification is size: population-based biobanks versus disease-oriented biobanks. The former are large-scale biobanks that store samples from a general population with the aim of studying the role of individual genetic susceptibility and exposure to external factors in the development of specific diseases by linking molecular data with other associated information; the latter stores biological samples from different sources, generally obtained from patients, which are important for the study of a disease, for example, cancer (Coppola et al., 2019). If the former enable the study of biomarkers of susceptibility and predisposition, and the latter permits the biomarkers of disease, there is a third category, epidemiological biobanks, which allow large-scale cohort studies to search for biomarkers of exposure and biological effects (Harris et al., 2012).

Another traditional approach of classifying biobanks has been according to the type of research carried out with biological samples: (a) population studies, (b) basic research; (c) associated with clinical trials; (d) translational studies; and (e) pathology archives. These latest collections, from diagnostic residual samples, as results of the large amounts of samples stored and the medical data associated with them, have become very attractive for biobanking. But also the secondary use of these samples for research purposes give rise to ethical challenges, since they are

used for a different purpose for which they were obtained and without prior explicit consent for that new purpose.

Since the traditional classification of biobanks are not precise enough to properly delimit the different categories of biobanks (Malsagova et al., 2020), it has been proposed to use functional criteria that allow better systematization and categorization of them, namely, depending on: the type of donor/participant, the collection methods and design (e.g. retrospective or prospective collection, size and scope), the characteristics of the biological samples (e.g. form of preservation of the biological sample, fixed, frozen, fresh, live, and desiccated), and the brand of the biobank based on the leadership of those leading it and the sponsors who support it as well as the intended users (e.g. individuals, often expert researchers and groups, and institutions) (Watson & Barnes, 2011).

This latter criterion is connected to one of the central issues in the ethical discussion about the operation of biobanks, whether they should be considered public goods, whether they are hosted or sponsored by public or private institutions (universities, research centers, hospitals, governments, international consortia). Biobanks as public goods is determined by their vocation to make samples available to the scientific community for all those projects that comply with the scientific and ethical conditions previously established by the biobank, following principles of transparency and public trust that, among other principles, are those that found the governance of biobanks in front of the participants and the community (Gille et al., 2020). Private initiatives of biobanks for commercial purposes, on the other hand, are not aligned with this logic of public good that is claimed for biobanks, and for this reason they have generated a profound ethical debate (Caulfield et al., 2014). An emblematic case of a private biobank is that of the company *23andMe*, whose business model is the sale of samples obtained from the services they provide through direct-to-consumer genetic tests (Caenazzo & Tozzo, 2020; Vähäkangas et al., 2021). Although one of the most sensitive issues in the ethical debate is the distrust in the public perception regarding the commercialization of samples by private biobanks, the increasing difficulty of funding and sustainability of public biobanks leads to the search for public/private alliances (Somiari & Somiari, 2015). Therefore, strategies are proposed to reduce public distrust, clarify the real perceptions of people, propose independent governance (Nicol et al., 2016) and "promote dialogue, both technical-scientific and ethical, essential between the public sector, the private sector and citizens to truly maximize transparency and public trust in both contexts" (Caenazzo & Tozzo, 2020).

Finally, we should refer to another category of biobanks that is becoming more and more significant due to the increase in data from whole genome sequencing (GWS) techniques. They are the so-called virtual biobanks, which are electronic repositories with the information on biological samples and their associated data, independent of the place where the physical biological samples are stored, information that can be shared in networks of national and international biobanks (De Souza & Greenspan, 2013; van Draanen et al., 2017). Because of the increased use of big data for research purposes, some scholars propose that biobanks should move from a sample-centric strategy to a data-centric strategy (Quinlan et al., 2015). To the

virtual biobanks, another recent category should be added, imaging biobanks that store data, metadata and image biomarkers, extracted from computerized tomography, magnetic resonance imaging, and positron emission tomography. This type of biobank allows radiomics, a field of medicine that consists of extracting a large number of features from medical images, using data characterization algorithms, one of whose relevant developments are "image biomarkers (a new class of biomarkers non-invasive) for physiological evaluation or pathological processes and therapeutic treatment" (Malsagova et al., 2020).

Each biobank categories have ELSI challenges, which we will examine throughout the different stage of biobank evolution, from the governance challenge stage to challenges for sustainable biobanking, passing through the stage of harmonization and collaboration networks. The ELSI aspects of biobanking comprises four broad topics: (1) Topics related to how biological materials are incorporated into the biobank and their use: samples donated directly to the biobank for research purposes or residual samples from clinical care for future use in research, as well as issues related to the informed consent of the donor (types of consent, information provided, right of withdrawal, participation of minors and use of samples of deceased persons, opt-in or opt-out policies, etc.). (2) Issues related to biobanks as institutions, such as authorization, registration, governance principles, management and quality standards, etc. (3) Issues related to the conditions of access by researchers to the samples and associated data of the biobank, which implies, for example, impartiality in access, commitments and responsibilities assumed in the material transfer agreement; and issues related to the ownership of biological materials and intellectual property derived from such materials, including custody issues, conflicts of interest, review committee, and regulation of intellectual property over human biological material. (4) Finally, issues related to the information collected and stored, as well as the rights of the donor to know the results of the research, access their data and be informed of the results relevant to their health (including an incidental findings policy), disclosure of results, confidentiality, data security measures and data protection –anonymization, pseudoanonymization, risks of re-identification, discrimination and stigmatization (Solbakk et al., 2004; Vähäkangas et al., 2021; Nicholas, 2022).

First Stage of Biobanks' Evolution: Governance's Challenges

The evolution of biobanks has been characterized by a constant challenge to traditional ethical principles and criteria of scientific research with human beings and their regulation. ELSI challenges of biobanks are related to the fact that these infrastructures enable the realization of multiple future research projects and in wide-ranging lines of research, with the use of samples and especially sensitive information, such as genetic data, which can be shared internationally, and whose specific purpose may not be known to the donor at the time of donation. The challenge is, then, to balance the enormous social value that biological material and

associated information has for research and the benefits for human health on a large scale, enhancing the quality of science and international collaboration, with the risks each individual donor in the samples is exposed to (Bledsoe, 2017).

This challenge is not an easy task, at least for two reasons making management and governance of biobanks provoke so much ethical and legal concern in the last two decades. First, they are infrastructure aimed at the future use of samples, stored indefinitely, which significantly increases the donor's loss of control. Second, with the digitalization of biological data, biobanks become custodians and responsible for large volumes of future genetic data, whose relevance, risk and impact are very difficult to predict if we consider the growing increase in interoperability between different databases worldwide (Vähäkangas et al., 2021; Akyüz et al., 2021). Under these circumstances, being able to guarantee and protect the basic ethical and legal principle in relation to research with human beings becomes much more complex and difficult, compared to the ethical review of research by specific projects: the interests of the individual (the so-called principle of moral primacy of the human being) –its autonomy, integrity, privacy, etc.– should prevail over the interests of science, (Różyńska, 2021).

If biobanking escapes the traditional logic of biomedical research governance –"one researcher, one project, one jurisdiction" (Kaye, 2011), which is subject to the prior supervision of an ethics committee that evaluates the requirements ethics to be met a priori by a specific project, as detailed in the protocol and informed consent–, the question arising is how the governance of biomedical research is reconfigured when the rights of the participants must be protected against future projects, not yet specified or determined, in relation to the use of biological samples and associated personal data, as well as their destination and the results that will be obtained from them. It is these new conditions of biomedical research with biobanks that have made us rethink the rights of the participating subjects and adapt them for the prospective use of their data and biological material. This includes right to participate in science and access to its benefits, right to consent, right to withdraw, rights of informational self-determination, privacy and confidentiality, and the right to know and not to know about genetic information, right to genetic non-discrimination and non-stigmatization, and even intellectual property rights.

The first stage of evolution of biobanks was oriented to take care of these moral and legal interests and the need for a new governance for biomedical research, and how to provide it with an ethical justification and an adequate regulatory framework. The foregoing included, mainly, an intense discussion on the modality of informed consent for biobanks, along with other topics such as the secondary use of samples and associated data, the effects to withdrawal of consent, privacy and confidentiality of data, the access to the results of the research and the return of the "incidental findings", the international data and samples sharing, as well as the ownership of the biological material.

Of all the topics, without a doubt the most discussed has been informed consent, because the traditional standard, namely the specific consent given for a specific project with a specific researcher, limits the practical possibility of authorizing the future use of samples in projects not yet specified with access for all those

researchers who request them. But, on the other hand, the ethical question arises to an open consent to indeterminate future uses that ends up blurring an essential element for free and voluntary participation: specific and adequate information about the objectives, scope, benefits and risks of the research in which the subject participates.

Informed Consent for Biobanking: Broad and Dynamic Consent

During the first decade of the 2000s, an intense debate began among experts in bioethics and regulation in biomedicine about the legitimacy of using broad consent instead of specific consent in biobank practice, with clear positions for (Hansson, 2005; Cambon Thomsen et al., 2007; Haga & Beskow, 2008; Helgesson, 2012) and against (Árnason, 2004; Caulfield, 2007; Greely, 2007; Caulfield & Kaye, 2009). Those who argued against claimed that broad consent is not valid consent because it does not allow informed autonomy to be exercised, since neither the objectives nor the risks of the research are specified. Those who argued in favor said that in order to justify research, the principle of autonomy of the participating subjects is not enough, it is necessary to appeal to other ethical principles. Both arguments answered the question of how to balance the public interest represented by the use of human biological material with the rights of donors.

In a very influential article in this debate, Hansson et al. (2006) argued that "broad consent and consent to future research studies are valid ethically and should be recommended for biobank research" as long as the following conditions are met: "personal information related to the research is handled safely, that donors of biological samples are granted the right to withdraw consent, and that every new study is approved by the ethics-review board" (p. 266). This last condition is important to reject the argument that broad consent is equivalent to blanket consent or open consent. If each investigation that uses samples from a biobank must go through the review of an ethics committee, then it is granted that it is not a blanket consent, that is, a consent that the donor grants only once authorizing future use and open of your samples and data without any supervision. Nor would broad consent consist of an open-ended permission without any limitation, nor would it be an open consent in which the donor authorizes their data to be made available to the world scientific community, anonymized or not (as in the initiatives HapMap, 1000 Genomes, and Personal Genome Project) (Rothstein et al., 2016). In addition, those who have argued in favor of broad consent add that biobanks operate under the logic of public good, following principles of equity and solidarity, therefore, in this context, the ethical framework of scientific research cannot be reduced to the individualistic view based on the principle of autonomy as argued by those who oppose broad consent (Knoppers, 2005; Chadwick & Berg, 2001).

In summary, the arguments to justify broad consent were based on three reasons: (i) practical reasons, since it would be impracticable to re-consent thousands of donors each time their samples are used in a specific research; (ii) biobanks are

intermediary tools at the service of the scientific community and the good of society that function as a public good, with open access to third parties to the samples they store; (iii) biobanks allow non-interventional studies of minimal risk. However, these same reasons have been criticized by those who questioning broad consent, considering its fragility to operate as a definitive ethical justification (Caulfield & Kaye, 2009).

After years of debate, the regulatory bodies and international guides were accepting the legitimacy of a broad consent that would allow a system of access and use of samples by any researcher, as long as this system is maintained under organizational measures that granted the rights of donors. In this sense it can be called a consent for the governance of the biobank. This was the policy that followed Council of Europe, in its Recommendation Rec(2006)4 of the Committee of Ministers to member states on research on biological materials of human origin, that considered a good practice to request broad consent when collecting material whose future use is not specified, but it should not be so broad that it becomes an "unconditional, blanket consent", for the same reason it suggests being as explicit as possible regarding future uses (Explanatory Memorandum 48). In the United States, the discussion and adoption of broad consent by experts and the regulator took longer. Scholars in 2015 reached a consensus that broad consent is ethically acceptable as long as it has ethical oversight from a committee for future projects that will use the samples and, where possible, mechanisms for maintaining contact and sharing communication with donors (Grady et al., 2015). Finally, Congress modified the Common Rule in 2018 incorporating an express rule on broad consent and the basic elements it must contain (45 CFR 46.116(d)).

The need to maintain contact with the donor, as a condition that legitimizes the consent for future use of the samples and associated data, justifies another form of consent that has been proposed for biobanks: dynamic consent. This form of consent uses digital tools to facilitate two-way communication between the participant and researchers, placing the participant at the center of decision-making. Those who promote this type of consent consider that this interface has an advantage over the broad consent model because: (i) allows participant to be consulted each time their samples and data are used; (ii) facilitates giving and withdrawal consent when circumstances change; (iii) provides a single record of the transactions and interactions that are maintained; (iv) allows participant to give different types of consent or ask for their opinion as new research projects are initiated or new ethical issues arise; (v) and, finally, the decisions made in the initial consent can be modified over time through this interface (Kaye et al., 2015; Budin-Ljøsne et al., 2017).

However, before the idea of this form of consent became widespread, empirical evidence showed that people preferred a single initial consent instead of expressing their will in successive instances (Lipworth et al., 2011). In another study, which compares broad consent with dynamic consent, the latter is criticized for the overload that implies in time, both for the participants and for the researchers, granting a new consent for each project, as well as criticizing due to the negative effect that it could have on participation by repeatedly exposing people in each consent to the complexities of research and the need for them to have an opinion and make a

decision about it (Steinsbekk et al., 2013). Dynamic consent has also been criticized because it can jeopardize the logic of public, collective and long-term good of biobanks, to the extent that the individual decisions of each participant for each project, by replacing the decision criteria of the committees of the biobank, could weaken its governance, which could be a risk, in turn, for the participants themselves. In addition, there is a risk that the research policy of a biobank is replaced by the sum of informed consents that were only given for a particular project; and, finally, if the dynamic consents include granting a broad consent within their options, it is contradictory, because precisely the latter was the ethical problem to be avoided (Soulier, 2019).

Secondary Use of Data and Biological Samples

There has also been discussion in the literature about what are the appropriate mechanisms to incorporate residual tissue collections obtained primarily for clinical care purposes into biobanks. These collections are of interest to biobanks because to the large number of samples they accumulate and the associated health data. The focus of the discussion has been on evaluating which is the most appropriate method to consent to the entry of residual samples into the biobank: opting-out (procedure under which the non-expression of will is treated as a sign of consent) or opting-out. in (procedure under which a person explicitly expresses his consent). While the consensus is that the opt-in method is preferable for research participation, both methods should be evaluated based on the kind of tissue and research in which they are to be used. Thus, it has been suggested that in certain situations the opt-in method is necessary: "(1) research with higher risks or increased burdens, (2) the use of controversial or high-impact techniques, (3) research on sensitive tissue, and (4) research involving vulnerable patients" (Giesbertz et al., 2012). These same authors have argued that the opt-out method is justifiable if it is used under certain conditions that give more guarantees to the potential donor, in which case the dichotomy between the two methods is less strong. The conditions they propose to be able to implement an opt-out system are: "(1) awareness has to be raised, (2) sufficient information has to be provided, and (3) a genuine possibility to object has to be offered" (Giesbertz et al., 2012). This system was adopted in the latest CIOMS Guidelines version of 2016 in guideline 11 collection, storage and use of biological materials and related data, which operates with the same conditions and restrictions indicated above for the opt-out.

The Right to Withdraw Consent

Other interest of the research participants whose exercise must be adapted to the biobank is the withdrawal of consent. The biobank should balance the conservation interest of its collections with the participant's right to withdraw their authorization to use their samples and associated data at any time. In fact, the nature of the operation of the biobank makes the exercise of the right of withdrawal different from what is done in traditional biomedical research, because, of course, the withdrawal can only be applied to future research, not to those in which they are being used samples and data or those that have already been used. When the data are entered to other data sets cannot be deleted, nor the withdrawal be extended to the data that is the result of research carried out. For the same reason, the way in which this option is communicated to the donor and how he can exercise it is relevant. One communication strategy is to signal to the donor their option to request the destruction or anonymization of the sample and associated data. In case of anonymization, the samples may be used without the possibility of linking them to the identity of the donor, to the extent that the code that could identify them has been eliminated. Another strategy is the staggered one, different from the previous "all or nothing" (Melham et al., 2014), which offers more options to the participant, and which has been the strategy adopted by the UK Biobank: (i) "no more contact" with the participant, but that their samples and associated data, and information from their clinical record, can continue to be used; (ii) "no further access" to the information in the clinical record, nor the possibility of contacting the participant, but authorizing the use of samples and data that were previously donated; (iii) "no more use" of the previously obtained samples and data, along with no contact or obtaining more information from the participant, therefore, the samples are destroyed and only the participant's information necessary for auditing is kept. Undoubtedly, a dynamic and continuous consent over time can facilitate the exercise of the right to withdrawal in a staggered manner.

Privacy and Confidentiality

The risks associated with the privacy of the subjects participating in a biobank, with the confidentiality and protection of their personal data associated with the samples, are one of the most sensitive and discussed ethical issues within the governance of a biobank, especially when the risk is associated with genetic data. The potential risk of malicious or improper use of personal data or the eventual risk of re-identification of the owner arises a set of obligations both for the data controller or data processor in the biobank and for the researchers who request them (Akyüz et al., 2021). The challenge for biobanks, when defining personal data protection duties, should be able to balance the collection and exchange of data and samples on a large scale with the way sensitive information is obtained and safeguarded, such

as genetic data and health data, respect the consent of the owner and his legal rights to data protection and non-genetic discrimination (Rothstein et al., 2016).

Although the irreversible anonymization of samples and data can be considered the safest way to protect privacy, this mechanism seriously limits the usefulness of biobanks. Because the research carried out with the samples will not be able to link a person's genetic and biological data with their health and epidemiological information associated with their samples, and thus be able to contact them again to update that information, request new consent or provide clinically relevant information. Therefore, irreversible anonymization does not guarantee the rights of the participants –to the return of results and relevant information, and to the withdrawal of consent, since it makes it impracticable– nor does it allow the operating logic of research with biobanks. (Eriksson & Helgesson, 2005). For these reasons, some legislations (e.g. Brazil and Mexico) does not allow the total de-identification of the samples, unless expressly authorized (Rothstein et al., 2016). So the way to properly guarantee the rights of the donor is to pseudo-anonymize their identified or identifiable data.

The terms to refer to the degrees of identification of personal data and the rules for their protection, their secondary use and international exchange, have been very varied among the different jurisdictions. This situation, in addition to confusion there are those who think that it has affected the international collaboration between biobanks (Knoppers et al., 2007). Hence the relevance of international standards to promote regulatory harmonization.

An example of international standards is the UNESCO International Declaration on Human Genetic Data (2003), which recognizes that human biological samples, to the extent that they are a data medium (genetic and proteomic) that can identify a person, must be treated under the same principles of personal data protection, for which it distinguishes the following categories: (i) data linked to an identifiable person (contain information, such as name, birth date and address, by which the person from whom the data were derived can be identified), (ii) data unlinked to an identifiable person (are not linked to an identifiable person, through the replacement of, or separation from, all identifying information about that person by use of a code) and (iii) data irretrievably unlinked to an identifiable person (cannot be linked to an identifiable person, through destruction of the link to any identifying information about the person who provided the sample), which cease to be personal data, unlike the first two that, according to the Declaration, "should be dealt with in accordance with the wishes of the person", that is, respecting their right to informational self-determination.

Another example is the Recommendation CM/ Rec(2016)6 of the Committee of Ministers to Member States on Research on Biological Materials of Human Origin that distinguishes data associated and dissociated from an identifiable person from irreversibly dissociated data, using the terms "identifiable biological materials" and "non-identifiable biological materials", respectively (article 3). Identifiable biological materials "are those biological materials which, alone or in combination with data, allow the identification of the persons from whom the materials have been removed, either directly or through the use of code(s)"; and in the latter case, that of

coding –or also called pseudonymization–, the Recommendation distinguishes between two situations: if the user of the biological materials may have direct access to the code(s) (coded sample) or if the code(s) may be under the control of a third party (reversibly anonymized samples). In contrast, non-identifiable or irreversibly dissociated samples "are those biological materials which, alone or in combination with data, do not allow, with reasonable efforts, the identification of the persons from whom the materials have been removed". In the latter situation, the reasonableness criterion means that "if the identification is not foreseen or expected in any case, and the appropriate technical measures (for example, encryption, irreversible random verification, etc.) have been adopted to prevent that happens, the information processed by the original data controller cannot be considered to refer to identified or identifiable natural persons" (Nicholas, 2022).

International Data Sharing

The protection of the privacy and confidentiality of the data associated with biological samples that are shared internationally has been one of the aspects of continuous ethical observation by international guidelines and by the regulation of the different jurisdictions. It is essential for biobanking to be able to enhance their stored biological resources through governance policies that ensure the international exchange of samples and associated data with adequate levels of security and data protection. However, the regulatory dispersion that exists in this issue and the lack of legal harmonization constitute one of the main difficulties that the international community of researchers faces (Rothstein et al., 2016).

The international recommendations of different organizations related to genomic research have tried to reduce this lack of harmonization with guidelines that support regulatory policies in this area. Along these lines, for example, the P3G-IPAC organization for international genomic research suggests introducing clauses in the informed consent in relation to international data sharing like that: "Data will be made available to other researchers around the world and used in unspecified future biomedical research in universities, hospitals, non-profit groups, companies, and government laboratories after approval. All researchers will have to respect the laws and ethical guidelines that apply to biomedical research" (Thorogood & Zawati, 2015). In addition, it suggests specifying in the consent the guarantees of privacy and access governance.

Another international organization that has promoted the culture of sharing genomic data is the Global Alliance for Genomic and Health (GA4GH), whose "Framework for Responsible Sharing of Genomic and Health-Related Data" requires researchers to provide transparent information on "data transfer to third parties; international transfer of data; terms of access; duration of data storage; identifiability of individuals and data and limits to anonymity or confidentiality of data; communication of results to individuals and/or groups; oversight of downstream uses of data; commercial involvement; proprietary claims; and processes of

withdrawal from data sharing" (https://www.ga4gh.org/). The logic of this framework is that privacy requirements are proportional to the types of data (identifiable, encrypted or anonymized) and the use that will be given, without prejudice to the fact that other kinds of risks and benefits are also considered for participants, researchers and society in general. In addition, given the impossibility of guaranteeing the absolute anonymity of data –especially, genomic data–, it is necessary for reasonable governance of international data exchange "a commitment by researchers to forgo any attempt to re-identify not expressly authorized by law" (Thorogood & Zawati, 2015). These same authors add that "addressing re-identification risk requires ongoing risk assessment, adaptive privacy safeguards, and more concerted oversight of access".

Communication of Results and Disclosure of Incidental Findings

Donor subjects have a right to information related to the biological samples and associated data. Within these information rights, the most sensitive to manage, as the literature has highlighted for some time (Clayton, 2008; Wolf et al., 2012; Clayton et al., 2013; Black et al., 2013; Appelbaum et al., 2014; Zawati & Knoppers, 2012) is that of the incidental findings that are found from the analyzes that are carried out on the samples, especially when techniques such as whole genome sequencing and whole exome sequencing are used, which allow obtaining information that goes beyond the primary objectives of the investigation. This right must be distinguished from other rights to information, namely, the right to know the general results of the research in which their samples are used, which is justified by the right to science and to enjoy the benefits of scientific progress and its applications, and the right of access to personal data, the latter emanates from their right to informational self-determination.

Donors are entitled to health information obtained from the analysis of samples consisting of the following aspects: (i) they refer to health data in a broad sense, including those that are relevant for taking reproductive decisions, (ii) the subject can choose whether or not to receive this information (right not to know), and (iii) the information may also be relevant to third parties. The foregoing leads to ethical and legal problems: first, the subject must receive information in the consent process that allows them to adequately exercise these rights; second, to eventually be able to rely on genetic counseling to communicate this health information; third, the need to communicate the information when it is relevant to health and determine who should communicate it; fourth, to determine the relevance of the information according to some criteria, such as the severity of the disease that is predicted with the information, if there is a possibility of intervention, and its analytical validity and clinical relevance.

One of the ethical problems that the literature addresses regarding incidental findings is the risk that the research purpose of biobanks will be confused by the participants with therapeutic or clinical purposes, which in the research ethics literature is has called therapeutic misconception. Another confusion that arise in the practice of managing these issues in biobanks is between the general return of research results and the delivery of individual results. For this reason, the literature recommends that there be clear definitions in this regard in biobank policies and well-established criteria for the return of incidental findings (Zawati & Knoppers, 2012). An example of governance policy in this area is the UK Biobank, which in its protocol establishes that "there may be occasions when staff consider there to be a professional or ethical obligation to draw attention to abnormal measurements (such as elevated blood pressure) or incidental findings (such as possible melanoma). In such circumstances, participants will be encouraged to contact a relevant health professional". In addition, it provides that participants will be given the results of reference laboratory tests prior to storage of a sample when this may indicate a serious disease for which intervention is possible. However, its policy states that no information, whether genetic or not, will be provided as a result of the analyses that are carried out after the registration of the subject in the biobank (Johnston & Kaye, 2014).

In comparative law, the criteria are not entirely clear and uniform regarding this communication obligation. Black et al., in a study addressing 23 laws, policies and guidelines of international, regional and national organizations that provide guidance or identify the need to disseminate the incidental findings to research participants, found little reference to how biobanks and researchers should bear the costs and funding of communicating incidental results. They therefore call on the research community and policy makers to reflect on the financial implications of ethical imposition of communicating incidental findings. International recommendations can help to promote better harmonization of the criteria for reporting incidental findings in biobank policies.

In the latest version of the CIOMS/WHO Guidelines (2016) a new recommendation is included in Guideline 11 collection, storage and use of biological materials and related data, which specifically proposes criteria for the return of results and disclosure of (un)solicited findings, which is a way of delimiting the ethical obligation and its costs, noting that: "In general, the three guiding principles for return of results need to be followed: results must have analytical validity, clinical significance and actionability to qualify for being returned. This implies that life-saving information and data of immediate clinical utility involving a significant health problem must be offered for disclosure, whereas information of uncertain scientific validity or clinical significance would not qualify for communication to the participant. The research ethics committee should also evaluate whether individual counseling is necessary when returning particular genetic findings. Some cases may require making an ethically responsible management plan for returning (un)solicited fndings".

However, this is still a widely debated topic in the different jurisdictions and biobank policies (De Clercq et al., 2017). It has been argued that, if the policy for

returning results in biobanks is not addressed clearly and specifically, establishing when, how and what type of results must be returned, the trust of donors may be compromised and thus affect the sustainability of biobanks (Cadigan et al., 2017). Although the debate about policies for returning results and, in particular, incidental findings, continues to evolve, there is at least consensus on the ethical obligation to return results that are clinically relevant and to promote better international harmonization and clear and specific policies for each biobank that guarantee transparency and trust in the community.

Second Stage of Evolution: Harmonization and Collaborative Networks

Biobanks are collaboration platforms that enhance and optimize their work through collaboration networks, which requires efforts to harmonization of technical, ethical and regulatory standards. Indeed, the development of biobanks, especially population biobanks, in recent decades has required greater global coordination and international harmonization of ethical and legal standards for the protection of donors, especially in privacy of genetic data, basically because this activity has been challenged by three trends: "1. Biobanks are storing and sharing more information as molecular sequencing becomes more affordable, researchers collect more clinical and epidemiological data on participants, and digital networks expand. 2. Biobanks are increasingly being used as "universal research infrastructures" accessed for broad, future uses by researchers from various fields, sectors, and nations. 3. The scale of biobanks and linkage between them is expanding to achieve the sample sizes needed to explore the complex causes of common diseases." (Thorogood & Zawati, 2015). However, this international collaborative effort to share samples and data from large populations, considered a scientific and ethical imperative aimed at promoting the common good of knowledge and people's health (Zawati et al., 2014), is hampered by the lack of common legal criteria, especially with regard to access to samples and data.

Although the regulatory strategies for the establish, organization and operation of biobanks are very different from one jurisdiction to another, two main can be found: (i) countries that opt for special legislation for biobanks; and (ii) countries that apply general legislation to the activity of biobanks, such as laws related to the use of tissues, data protection laws, among others, and complement the legal regulation with specific national guidelines for biobanks. Compared with national legislation, regional and international guides have the mission of establishing common criteria that, although they are not legally binding (soft law), can guide national legislation. However, and despite the enormous proliferation of this type of international guides related to good practices in biobanks, in practice they have not been able to promote regulatory harmonization due to the particularities of each national

legislation and local ethical practices regarding the use of human biological material, the culture of data protection, confidentiality and privacy.

Below we present the analysis of the two regulatory strategies at the level of national law for the governance of biobanks, as well as the international instruments aimed at harmonizing legislation and the challenges they have entailed, ending with the initiatives of international collaboration networks of biobanks, which develop their own methods and guidelines of good practices for their operation as a mechanism to improve interoperability between biobanks.

Countries with Specific Legislation on Biobanks

The strategy of establishing a specific legal for biobanks was adopted early by some European countries that initiated a national population biobank policy (Zika et al., 2010; Zawati et al., 2014; Beier & Lenk, 2015; Chalmers, 2015). The first countries to enact special laws to regulate the activity of biobanks with special laws and regulations were: Iceland (The Biobanks and Health Databanks Act No. 110/2000; Regulations on the Keeping and Utilization of Biological Samples in Biobanks. No. 134/2001), Estonia (Human Genes Research Act, 2000), Sweden (Biomedical in Medical Care Act No. 297/2002), Norway (Act Relating to Biobanks No. 12/2003, replaced by Act on medical and health research, No. 44, 2008), Spain (Law 14/2007 on Biomedical Research, 2007; Regulations N° 1716/2011 which establishes the basic requirements for the authorization and operation of biobanks for biomedical research purposes and for the treatment of biological samples of human origin, and regulates the operation and organization of the National Registry of Biobanks for biomedical research), Belgium (Loi relative à l'obtention et à l'utilisation de materiel corporel humain destiné à des applications Médicales humaines ou à des fins de recherché scientifique, No. 18385, 2008). Just after, are added Finland (Biobank Act No. 688/2012) and Singapore (Human Biomedical Research Act No. 29/2015).

In the legislation of these countries there are some common elements such as the regulatory control of the activity of biobanks, the protection of personal data, the rules of international samples and data sharing, rules of informed consent, among others. Regarding the establish of biobanks, these countries, in general, set regulated and detailed procedures for the authorization and establishment of biobanks, with an authorization and registration procedure before the competent authorities in health, which, therefore, in general, it is also a supervisory authority. In addition, the sponsorship of the biobank belongs to the government or public bodies and entities linked or dependent on it (Spain), or a public university (Estonia).

One of the essential issues that regulate these laws is informed consent, establishing as essential elements of consent the purpose of the biobank and the express declaration of the granting of samples. However, when specifying in the law the requirements that consent must satisfy, some countries assume extremely rigorous models, while other countries simply establish the general requirements that must be met in its granting. In general, regarding the waiver to informed consent, the

cases covered by the legislation are associated with hypotheses of an excessive effort to re-contact or obtain consent to obtain the sample. Another exception to informed consent is established in the event that the new use of the sample is not suitable for the purpose for which it was obtained. In this case, the data that allows identifying the donor of the sample is dissociated, in such a way that the use of the sample is possible without being associated with the donor whose consent could not be obtained or obtained again. In these exceptional cases, it is necessary to have authorization from the Scientific Committee associated with the biobank or from the corresponding authority.

The option of withdrawal of consent is considered in all these laws. Some legislations have rules that require the destruction of samples after withdrawal consent (e.g. Iceland and Sweden). An important exception to the destruction of the samples that would proceed after the withdrawal of consent is the case of Norway, which requires that the corresponding sample has been previously anonymized (Zawati et al., 2014).

In general, the laws require the need to adopt adequate security measures for the protection of biological samples and associated data that are stored in the biobank and usually refer to data protection law. A general duty of codification of the information related to the samples is required, and the data and information obtained from the samples must be safeguarded. In addition, in certain cases, the drawing up of a reference to the administrative or technical regulations issued by a competent body is verified (e.g., Spain and Iceland).

Although these biobank laws regarding international sharing of data and samples have features in common, not all laws set identical criteria in this regard. In some cases, it is necessary to request a transfer authorization from the health authority that supervises the country's biobanks (Iceland, Sweden, Norway); in other cases, the authorization of the corresponding IRB is required (Spain, Finland). Not only is the authorization of the corresponding supervisor required, in other cases the sponsorship of a national institution is also required. In addition, conditions are established for the return or destruction of samples that have been transferred abroad (Sweden).

In relation to the communication of incidental findings, few countries consider legal regulations that require their communication. These legislations opt for the will expressed in the consent (Spain), that is, consent or not of the donor to communicate them in case they appear, or they opt to require a communication protocol for these cases (Singapore).

The regulatory strategy based on a special law, although it can produce legal certainty in the operation of biobanks and express guarantees of the rights of donors, has its limitations. First, because the particularities of the legislative tradition of each country make it more difficult international regulatory harmonization. Second, it is not enough to generate transparency and public trust. Third, adaptive capacity of the legislation to changes is weaker, therefore, it is crucial that regulator does not produce very exhaustive rules, restricting space for recommendations.

Countries with General Legislation Applicable to Biobanks

These countries choose to resolve the regulatory issues of biobanks through guides or orientations (soft law) that complement the general legislation applicable to these matters, for example, relating to biomedical research, use of tissues and data protection. The common law countries that opt for this regulatory strategy are the United Kingdom, the United States and Australia.

In the case of the United Kingdom, once the UK Biobank was created in 2002, a law of general application was enacted (Human Tissue Act [2004]), which contemplates the establishment of the Human Tissue Authority, an institution in charge of authorizing, through licenses to the different biobanks, the collection, storage and use of human tissues. Other laws applicable to biobanking are the Data Protection Act (1998), the Human Rights Act 1998, the Mental Capacity Act (2005), the National Health Service Act (2006), the Freedom of Information Act (2000), among others. For lack of specific legislation, there are many guidelines. In the case of the UK Biobank, its sponsors, the Wellcome Trust and Medical Research Council, have developed an "Ethics and Governance Framework (EGF) and established their own internal monitoring body, the Ethics and Governance Council (EGC), to legitimize and communicate the governance of UK Biobank to ensure it is managed in the public interest" (Kaye et al., 2016). Regarding data sharing policy, Wellcome Trust has issued its own Policy on Data Management and Sharing (updated 2017).

In the United States, the regulatory strategy was also not along the lines of a federal law that regulates biobanks, but through the application of different general laws that are extended to biobanking, such as the Common Rule, 45 CFR § 46, Health Insurance Portability and Accountability Act (1996), Standards for Privacy of Individually Identifiable Health Information (referred to as the 'Privacy Rule'), and the personal data law, Privacy Act (1974). Other laws that apply to biobank activity in the United States are the Stem Cell Therapeutic and Research Act (2005) and the Genetic Information Nondiscrimination Act (2008). However, the lack of specific legislation for biobanks has been criticized because it is cumbersome to apply the general rules for biobanking and also because they do not adequately protect personal data associated with samples through de-identification as required by the standard of European countries (Rothstein et al., 2016; Harrell & Rothstein, 2016). The most widely supported guideline is the National Cancer Institute's Best Practices for Biospecimens Resources (2007, 2011).

Although Australia does not have formal biobanking legislation, the main national funding agency, the National Health and Medical Research Council, has issued different guidelines and policies in this area. Most Australian biobanks are part of the Australasian Biospecimens Network, which has issued its own guidelines, the ABN Network Biorepository Protocols (Chalmers, 2015). Among the most outstanding particular aspects of the Australian regulatory standard are the considerations related to the protection of its original peoples. These are based on the fact that in its population it is possible to find genetic heritage of native peoples of about 40,000 years old. As an example, can be mentioned the report published by

the NHMRC entitled *Ethical conduct in research with Aboriginal and Torres Strait Islander Peoples and communities: Guidelines for researchers and stakeholders* (2018). An analogous case is New Zealand. Indeed, the Māori & Indigenous Governance Center of the University of Waikato, New Zealand, has published the *Guidelines for Biobanking with Māori* (2016), which establish special considerations aimed at protecting the population of Māori origin.

International and Regional Guidelines on Biobanking

At the international level, the first documents dealing with consensus standards for the management and transfer of biological material and genomic data were those issued by the Human Genome Organization's (HUGO): Principles Agreed at the First International Strategy Meeting on Human Genome Sequencing (1996) (Bermuda Principles); Statement on DNA Sampling: Control and Access (1998); Statement on Human Genomic Databases (2002); Sharing Data from Large-Scale Biological Research Projects: A System of Tripartite Responsibility (2003).

Around those same years, UNESCO was especially concerned with developing international human rights law relating to the human genome and genetic data, first with the Universal Declaration on the Human Genome and Human Rights (1997), and then with a more specific instrument that came to complement the previous one, the International Declaration on Human Genetic Data (2003), which regulates biological samples understood as support for personal data (genetic and proteomic data) and with the condition of personal data. This statement, along with protecting the privacy and security of donor subjects, provides that the principle of free, prior and informed consent allows national legislation to establish exceptions based on the relevance of the data that may be obtained for medical research or scientific, or for public health. And regarding the international exchange of samples and data, it establishes that "in accordance with their domestic law and international agreements, the crossborder flow of human genetic data, human proteomic data and biological samples so as to foster international medical and scientific cooperation and ensure fair access to these data".

Without a doubt, the recommendations of international organizations that have had the greatest impact are the Guidelines on Human Biobanks and Genetic Research Databases (HBGRD) published in 2009 by the Organization for Economic Co-operation and Development (OECD), which among its general recommendations is to promote that data access policies are fair, transparent and do not limit research. Likewise, a broad expert consensus has had a more recent guideline, that of the Council for International Organizations of Medical Sciences (CIOMS) in collaboration with the World Health Organization (WHO), International Ethical Guidelines for Health-related Research Involving Humans, Fourth Edition (2016), which in its guideline 11, storage and use of biological materials and related data, highlights substantive issues of biobank governance. First of all, this guideline highlights that broad consent in research is acceptable, which, although it allows

different future uses of the sample, requires certain restrictions for use, differentiating from blanket consent. Also, the guidelines highlight the need for institutions that collect biological samples and related data to have a governance system that allows them to request authorizations for the future use of materials for research purposes. Governance systems must safeguard the confidentiality of the link between samples and personal identifiers of donors. Likewise, they must comply with principles of transparency and accountability within which the participation of patient groups and the community in general must be enabled, as well as having appropriate mechanisms to keep participants informed of the results of the investigation. Other relevant aspects of this guideline point to the transfer of samples abroad, indicating that it must be done through a Material Transfer Agreement (MTA), which specifies the variety and duration of use, and what must happen at the end of the period usage, among other things.

At the European level, the Council of Europe has issued two recommendations, in order to harmonize the legislation of the member countries, the first was Recommendation Rec(2006)4 of the Committee of Ministers to Member States on Research on Biological Materials of Human Origin (2006), which was superseded by the Recommendation CM/Rec(2016)6 that establishes the conditions for obtaining and storing materials for future research, as well as for their use in specific research projects, in particular as regards regarding adequate information and the consent of interested parties, with its own chapter for the governance of collections.

The World Medical Association (WMA), for its part, in 2002 adopted a declaration on this subject, which was revised in 2016, at the 67th WMA General Assembly, Taipei, Taiwan, entitled Declaration of Taipei on Ethical Considerations regarding Health Databases and Biobanks. The specific statement, within its ethical principles, what information is necessary to be able to request a broad consent, in addition to establishing the basic principles for the governance of biobanks: protection of individuals, transparency, participation and inclusion and accountability, and these principles adds the necessary elements for a governance regime.

Although the binding force of international or regional guidelines depends on the issuing agency, they are all soft law, therefore, they cannot be used in case of conflict with local legal provisions, which, eventually, can be very restrictive for biobanking. Another limitation is the diversity of sources from which these guidelines come, which can often contradict each other. For this reason, other regulatory strategies that depend on the initiatives of the biobanks themselves to create national or international collaboration networks that have their own operating standards are gaining strength.

Biobanks Networks

Biobank networks began to form to address the difficulties of operating biobanks unconnectedly. Difficulties include "insufficient samples to conduct research on rarer diseases; inadequate infrastructure to process, store and retrieve samples to meet the necessary quality standards for research; cost of establishing and maintaining a large enough resource over the long term, and satisfying legal, ethics and governance requirements" (Shickle et al., 2010).

Although biobank networks are a way to promote and enhance the greater use of samples to reach a size necessary for the validity of the research and avoid bias, they maintain regulatory challenges such as having standardized technical procedures, a common quality control programs; homogeneous ethical requirements and an open policy for sharing. Therefore, biobank networks manage to harmonize their operation, rather than with a regulation strategy like the ones we saw in the previous paragraphs –special legislation or guidelines or national or international policies–, agreeing on common criteria of methods, approaches and tools for functionality.

One of the first collaboration strategies between biobanks was through the European initiative Promoting Harmonization of Epidemiological Biobanks in Europe (PHOEBE), which lasted until 2009. Until today, there is another collaboration initiative at European level, implemented as of 2013, Biomolecular Resources Research Infrastructure (BBMRI), whose main objective "was to develop an information technology concept for the exchange of data between biobanks (at national and European levels) and strategies for biobank material quality management, and also to present a positive and transparent image of biobanking" (Chalmers et al., 2016). It is currently a pan-European infrastructure of national biobank networks that is part of the European Research Infrastructure Consortium (ERIC), defined as a federated research infrastructure of biobanks and biomolecular resources that provides expertise and services –management services, support with ethical, legal and societal issues, and a number of online tools and software solutions for biobankers and researchers– in order to facilitate the use of European sample collections and data for the benefit of human health. Another federated initiative of European biobanks, dedicated to scientists conducting research on rare diseases, is EuroBioBank, a biobank network of RD-Connect.

There are also other international organizations that have played an important role in standardizing preservation and storage material from biobank. One of them is the International Society for Biological and Environmental Repositories (ISBER), whose mission is providing training and governance resources for human specimen repositories, through the ISBER Best Practices: Recommendations for Repositories, which provides standardized terminology describing the level of identifiability of samples. Another standardization initiative was the Public Population Project in Genomics and Society (P3G), an international consortium made up of not-for-profit organizations that conduct, use or collaborate with health studies, biobanks, and research databases.

At the level of national biobank networks, it is worth highlighting the Canadian Tumor Repository Network (CTRNet), the Australasian Biospecimen Network Association (ABNA), which includes biobanks across Australia and New Zealand, and Confederation of Cancer Biobanks (CCB), UK, all federated biobank networks. Other national networks instead follow a centralized model such as Kathleen Cuningham Consortium for Research into Familial Breast Cancer (kConfab, Australia), onCore UK (UK), Singapore Tissue Network, UK Biobank (Vaught et al., 2009). The review of international biobanks and networks carried out by Vaught et al. was repeated 10 years later, in which 12 of the 16 biobanks and networks reviewed were maintained, concluding that, despite "changes to their operation models or through diversification of their activities", in his opinion "one thing remains certain: our biomedical research community will still require the systematic collection and distribution of human tissue specimen from donors to scientists if we are going to continue to build knowledge about human disease and its consequences" (Devereux et al., 2019).

Third Stage of Evolution: Challenges for Sustainable Biobanking

Sustainability in the field of biobanks is a highly debated issue as a result to the implications that this activity has, from an ethical, legal and social point of view, since very relevant public interests are at stake, such as the health of the population and the generation of knowledge with high quality standards. In addition, the particularity of how biobanks work makes them very different from other research support structures, to the extent that they must take on many challenges, such as the ever-increasing complexity of sample storage and recovery, the management and integration of data and the establishment of common platforms in a global context (Karimi-Busheri & Rasouli-Nia, 2015).

Sustainability Problems

As Watson et al. have pointed out, "the topic of sustainability is challenging for the discipline of biobanking for several major reasons: the diversity in the biobanking landscape, the different purposes of biobanks, the fact that biobanks are dissimilar to other research infrastructures and the absence of universally understood or applicable value metrics for funders and other stakeholders" (2014). Without a doubt, it is essential to consider that the different types of biobanks (population versus specific pathologies or clinical study cohorts versus biomedical study cohorts) differ with respect to their sustainability plan as consequence to certain particular characteristics of each one (types of strategic collections, informed consent, participants,

samples and associated data, infrastructure, services, associated users, case monitoring, etc.) that are often not considered by stakeholders (Husedzinovic et al., 2015).

In this operating scenario of biobanks, the concept of sustainability applied to them cannot be reduced only to self-financing, other dimensions must be considered beyond the financial one, such as the operational and social dimension (Watson et al., 2014). Without question, the financial aspect of biobanking is very relevant, but at the same time complex. There is evidence that shows that the recovery of costs for the transfer of samples or the commercialization of products or services are not enough to achieve and maintain sustainability (Chalmers et al., 2016). This situation has led biobanks or biobank networks to seek new sources of long-term sustainability, which has apparently achieved a balance between public and private contributions (Doucet et al., 2017).

However, the debate continues about whether biobanks should be self-sustaining infrastructures through the strategy of giving impetus to market priorities (commercial patents) that seek to quickly bring out medical products and therapies. But it is clear that, during all this time of evolution of biobanks, these are platforms with a social value that goes beyond the exclusive purposes of profit. There are initiatives carried out by biobanks that are of interest to society as a whole, for example, if we think about the usefulness of generating anonymized health data sets to create virtual populations on which treatments and interventions can be modeled by computer of different types, as well as the usefulness of promoting the interoperability of data sets and sample collections for research purposes, or integrated in health care that require longitudinal samples of patients for permanent monitoring (Doucet et al., 2017). Therefore, the challenge is not only to have metrics to measure the sustainability of biobanks adjusted to the type of biobank (i.e., user, size, type) and taking into account the value to society, but also to continually evaluate new metrics that integrates apparently incompatible interests between sponsors, researchers, participants and the community in general, to approach a more real and adequate measure of the value of biobanks (Chalmers et al., 2016).

Dimensions of Biobank Sustainability

The sustainability of a biobank requires a balance between the social, operational and financial dimensions in the context of its own work (Watson et al., 2014). These dimensions have a close interaction and dependence on each other. For example, operational aspects are directly related to trust and acceptability by stakeholders, which means that following international biobank regulations and accreditations has an impact both technically and socially (Luna Puerta et al., 2020).

The operational dimension (efficiency) includes aspects of operational and organizational management, definition of policies and structure of a biobank. In turn, this dimension includes three points: (1) Entry efficiency means defining a participant enrollment program and a sample capture and storage system. (2) Internal efficiency has to do with operational harmonization according to good international

biobanking practices. Some examples of harmonization are: (i) sample exchange and quality: SPREC (Lehmann et al., 2012) and/or BRISQ (Moore et al., 2012) standard quality indicators for biospecimens that allow interoperability and standard *College of American Pathologists* (CAP) (Hainaut et al., 2009) that allows determining quality control in tissue samples; (ii) data exchange and transmission: adoption of integrative interoperable systems in accordance with The FAIR guides principles (Findable, Accessible, Interoperable, Reusable) (Wilkinson et al., 2016). (3) Output efficiency points to two actions: evaluating response capacity, for example, measuring user satisfaction, and having a broad catalog of services, biospecimens, and biomaterials.

The social dimension (stakeholder) refers to the relationship and interaction that a biobank establishes with the different stakeholders and also involves all aspects related to the ethical, legal and social implications (ELSI) that are the responsibility of the activity of biobanks (Bjugn & Casati, 2012). This dimension includes acceptability and assurance of standards. The first includes (i) guaranteeing compliance with the ethical-legal approvals for the biobank and associated projects, and (ii) engagement of people: transparent and participatory governance, generating dissemination and education activities, involving the patient in their follow-up, etc. (Mitchell et al., 2015). The second includes (i) adherence to good biobanking practices, obtaining certifications and accreditations (CAP, ISO, ISBER, etc.), quality program, etc., and (ii) training and education in biobanking, using local capacities, internships and international courses (Kinkorová, 2021).

The financial dimension (value) is related to the availability of resources and how these resources are obtained and used, which includes the business plan and model, the offer of services and products, and the sources of financing. This dimension includes the following points: (i) brand strategy that includes preparing an academic, marketing, business development plan, etc., constantly re-evaluating the development plan, and establishing a user rate (stratified or differentiated); (ii) stakeholder need includes, first, recognizing interests and needs of the community, scientific world, biotechnology and health industry, and second, defining strategic collections according to country and regional needs, according to the type of biobank that make up the Network and to associate researchers, etc.; brand recognition includes, first, disseminating the value of the biobank with all stakeholders, and second, measuring the value and impact of the biobank: generation of collaborations, publications, number of master's and doctoral theses, associated awarded projects, patents, etc.

Final Remarks

After more than 20 years of operation of research biobanks, despite constant ethical, legal and social challenges, the recognition of social value that these infrastructures have for the generation of knowledge applied to the field of genomic, post-genomic, and personalized medicine, as well as global or planetary health challenges, has not

declined. Likewise, biobanking is promoting a culture of international collaborative research that leads to a new paradigm regarding the assessment of risks and benefits of people's participation in research, community engagement, and the role of the association of public and private actors in promoting science.

I have stated that the shift from the logic of biomedical research "one researcher, one project, one jurisdiction" to a logic of research using future samples for many lines of research and shared internationally, has not only meant reconfiguring the mechanisms for protecting the interests of research subjects (informed consent, protection of privacy, access to information, etc.) focused on their individual decisions, but also to introduce the idea of governance of long-term research infrastructures, which should take into account broader health needs of the population. The latter highlights that biobanks are intermediary tools at the service of the scientific community and the good of society that function as a public good.

At the same time, the evolution of biobanking as a consequence of the increased use of genome-wide sequencing techniques and the importance the use of large amounts of data gains, shows that it is crucial to constantly review governance criteria to address new risks. The potential of these risks affecting the privacy control dimensions and the growing importance of international sample and data sharing, further stresses the demand for international regulatory harmonization criteria and commonly accepted good practices. Finally, I affirm that the ability of the global research ecosystem to adapt to these new risks depends on a systemic approach that understands the viability of the public value that biobanks have for society with an always renewed view of the three dimensions of sustainability.

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