

Review Article

Fundamental principles of human biobank development

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ABSTRACT

Biobanks are currently changing the face of modern medicine. The systematic collection and storage of samples of biological material and associated clinical data is revolutionizing biomedical research. Biobanks are extremely useful in the study of multi-factorial diseases, such as cancer and diabetes. They can be used to discover particular variations of diseases or novel therapeutic targets, and thus accelerate drug discovery in the scope of personalized medicine. However, human biobank development also presents a number of legal and ethical challenges, as well as key governance issues that

ought to be resolved, in order to achieve a satisfying level of political, financial and public acceptance. This paper discusses these topics by emphasizing in the European landscape, as exemplified by the Biobanking and Biomolecular Resources Research Infrastructure (BBMRI) initiative. Aspects of patient education and the role of primary health practitioners in facilitating the process are also contemplated.

Keywords: Biobanking, governance, ethics, quality assurance, data management

What do we know?

Public contributions to medical research are necessary for the advancement of science. Donation of biospecimens for the creation of biobanks is voluntary and does not affect a patient's treatment or clinical outcome. Several ethical and legal issues remain to be resolved, as regards the collection of biological material. Primary health practitioners have an important role to play in the process of informing patients, as regards personal rights and benefits, as well as the long-term potential of biobanking for both science and community.

What does this paper add?

Public awareness and acceptance of biobanks is required for the success of biomedical research. Initiatives like the BBMRI project provide organizational support that guarantee quality management of biospecimens and protection of privacy rights. These new technologies are expected to boost biomedical research and improve healthcare in the near future.

Introduction

Biobanking has been characterized as one of the top ten ideas changing the world right now, due to its potential of leading to personalized medicine.¹ Biobanks are necessary for identifying the genetic factors that cause disease, as well in advancing our understanding of how genetics interact with environmental influences.^{2,3} The concept of biobanking is that via genomic and proteomic analysis, each patient can be treated with a customized therapy, taking into account the genetic idiosyncrasy and unique susceptibility to disease.⁴

Different terms have been used to describe biological materials collection, such as “biorepositories”, “genetic databases” or “human research databases”. These are all synonyms to “biobanking”, which are nowadays more commonly used.^{5,6} In the array of terminology, the European Council has recently defined biobanking as the “collection of biological

*materials which has a population basis, it is established to supply biological materials or data for multiple future research projects, contains biological materials and associated personal data that may include or may be linked to genealogical, medical and lifestyle data, it may be regularly updated and receives and supplies materials in an organized manner”.*⁷

This definition underlies the marked heterogeneity of biobanks as a result of size, research design, types of biological samples collected and the disease/research focus (Table 1). The samples collected in biobanks may be derived from the general population or from a particular subset of the population, such as patients burdened with certain pathologies.⁸ In essence, biobanks are classified by purpose or design in two main categories, namely: (i) *disease-oriented biobanks* that collect samples from patients suffering from a specific condition, with or without collection of healthy controls, in order to search for biomarkers that are linked to disease manifestation and (ii) *population-*

Table 1. Terms and definitions of biobanking.

<p>Sample collection: Collection of biological material based on clinical and biological characteristics for research purposes.</p> <p>Subject: A living person, a patient or healthy control, from whom an investigator conducting research is collecting information through intervention and/or interaction.</p> <p>Biospecimen: A quantity of tissue, blood, urine or other biological material used for diagnosis and analysis. A single biopsy may generate many biological samples, including multiple paraffin blocks or frozen biological samples. A sample may include everything from subcellular structures (DNA) to cells, tissues (bones, muscles, connective tissue and skin), organs (eg liver, bladder, heart, kidney), blood, gametes (sperm and ova), embryos, fetal tissue, and waste (urine, feces, sweat, hair and nail pieces, aborted placenta and epithelial cells). As established, by the International Declaration of Genetic Data adopted by UNESCO, the biological sample is any sample of biological material in which nucleic acids are present and which contains the characteristic genetic makeup of an individual (Article 2. iv). The declaration applies to the samples before and after analysis.</p> <p>Tissue: Generally refers to a biological collection of cells and the extracellular matrix and/or intercellular substances that surround them. The term “tissue” often refers to a solid tissue from a solid organ. Nevertheless, as tissue can also be defined the broad collection of cells and intercellular substances (e.g. body fluids, such as blood).</p>
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based biobanks that collect samples from large numbers of people who act as volunteers, whether healthy or not, to search for biological markers responsible for susceptibility to specific diseases in the general population.^{9,10}

A successful example of a population-based biobank is the UK National Biobank, which has collected biological specimens and associated data from over 500,000 participants.¹¹ In 2008, a pan-European project called BBMRI (Biobanking and Biomolecular Resources Research Infrastructure) was established, in order to promote the cohesion of the European biobanking community and make existing high quality biological resources available for health-associated research institutions across Europe.¹²

Practical usefulness of biobanks: the BBMRI paradigm

Progress in medicine depends on innovation and application of laboratory findings to clinical practice. In order to transpose from laboratory discovery to medical application, research researchers depend on access to human biological samples.¹³ In this direction, biobanks have the potential to accelerate and further facilitate science innovation. Studies on diseases are often limited by the difficulty in recruiting sufficient numbers of cases within one collection site. This is particularly true for rare diseases, where efficient therapies are scarce and limited to only but a few exceptional conditions.¹⁴ In this scope, the emergence of biobanks can boost basic research and drug discovery.

Networking between biobanks offers the potential of flow of information, knowledge and biological materials across different centers, provided that all contributing parties adopt common practices for the collection, storing and labeling of samples, as well as for data management and manipulation.^{15,16} Biobanks are capable of facilitating these exchanges by providing the appropriate background and infrastructure for the successful implementation of multicenter research.¹⁷ The European Strategic Forum on Research Infrastructures (ESFRI) has developed and coordinates the BBMRI project, which is aiming to create a manageable network that accommodates all existing biobanks and support the establishment of new biobanks in the coming years.¹⁸

This network will bring together European Biobanks,

Molecular Research Laboratories and Bioinformatics Centers and will help connect information in accompanying samples and clinical databases.¹⁹ Public and private institutions (universities, research centers, hospitals, and corporations) are participating with samples, methodological tools and other expertise. BBMRI aims to harmonize standards concerning the collection, storage and analysis of samples, synchronize data collection and related infrastructure for databases, provide moral and legal guidance and create a sustainable financing environment for biobanks. An interactive list of associated biobanks was created during the preparatory phase of BBMRI, which included 250 centers from 21 European countries and provided more than 16 million samples for research purposes in the international community.²⁰ This co-operate work dramatically increases statistical power and enables “big-data” analysis by high-throughput screening technologies.

Projects like this are no doubt a gigantic leap into the face of translational medicine, enabling coherence and diversity across many disciplines, and the incorporation of various ethnic and genetic backgrounds. Management of private genetic information however, raises the need of strict regulative and organizational control. This reflects upon governance issues that take into consideration all legal, ethical and social constrains.

Aspects of biobank governance

Governance is broadly defined as the management of interdependencies. This refers to the organization spectrum under which a large set of interacting components meet, including decision-makers, institutions and policies, procedures and practitioners.²¹ The advantages of a successful biobank governance system is uniformity and quality assurance, efficiency of predefined rules, practice of research according to ethics and laws and transparency in decision making.²²

In this scope, significant challenges are presented. A legal framework applicable for all biobanks is currently missing and biobanks need to conform to national laws that are not always clear.²³ Discrepancies in legislation between different countries may hinder effective collaboration of biobanks and network development, debilitate organizational schemes and compromise data protection and biomaterial collection.²⁴ Several measures have been applied in order to overcome these obstacles. Member states of the European Union, for example,

have decided to develop a common legal framework for biobanking that effectively promotes the cooperation between parties and protects the participant's fundamental rights.²⁵

Approval by ethic committees is an indispensable provision for biobank establishment. However, the fact that licensing bodies only have limited authority confined to their jurisdiction, may stand as an obstacle to international collaboration.²⁶ For example, no mutual mechanism of ethics committee decisions exists and approval must be obtained for each participating institution at the national or county level. National authorities are encouraged to collaborate in this direction, in order to avoid unnecessary multiplication of compliance requirements.²⁷

Since the public actively offers specimens to biobanks, social partners' engagement into governance issues is essential. However, public awareness of biobanks' necessity is circumstantial. Only 1/3 of the European population is familiar with the term "*biobank*", yet public awareness and participation is mandatory for long-term survival of biobanks.²⁸ In some cases, public support and participation has been inspired by principles of social progress and solidarity, however this is not always the case.^{29,30}

Science and community have to cooperate on this matter. Longitudinal clinical data collection is often necessary for successful implementation of research projects.³¹ This aspires a long-term relationship between researchers and participants where the establishment of trust is a key element.³² Patients need to know what scientists are using their specimens for and what are the expected results, in order to agree to participate. For this reason biobanks must be supported professionally, in a multi-disciplinary fashion (including doctors, nurses, laboratory technicians, information technology experts, social scientists and psychologists).³³

Custodians have the responsibility for operations, compliance with best practices and regulations, as well as receiving, processing and responding to requests concerning access to stored samples. Successful management ensures long-term establishment of public trust.³⁴ Moreover, it is crucial to set up guidelines for the distribution and sharing of specimens and related data that comply with local, national and international laws, ethical norms and security of intellectual property rights, as well as to ensure the availability of data and materials to the wider scientific community and provide equal right of access to researchers.³⁵

It is generally thought that people are more likely to donate samples in a biobank if it is publically funded.³⁶ In this direction, the use of biobanks for clinical care and not only for research, could be plausible way for preserving fiscal sustainability without compromising financial viability.³⁷ This idea, however, is not without bioethical limitations.

Ethical issues concerning biobanking

Biobank researchers continuously face the following dilemma: on one hand the demand of the society for better, more effective treatment options, and on the other concerns about privacy. Biobank research involves risks concerning personal information related or derived from donated samples that may be misused and thus undermine privacy, autonomy,

personal integrity and confidentiality of research subjects.³⁸ Data "*anonymization*" instead of "*pseudonymization*" is not always an effective solution and raises ethical issues, such as the return of important clinical or genetic information to the individuals who donated their samples, hence depriving them of the right to benefit from their own participation.³⁹

When human biological materials are collected, it is obligatory to ask individuals to give their informed consent.⁴⁰ Legitimate processing principles of the European Data Protection Directive (95/46/EC) determine that the individual should be informed adequately about the kind of information that is being released, the acceptors of data and the purpose of its procession, in order to agree to participate.⁴¹ Central to the consent process is informing the subject on the potential benefits and risks, the methods and the demands of the researcher, as well as the possible research outcomes. Any inconvenience, psychological distress, return of information and postmortem research issues must be clearly demonstrated in the consenting process, along with full privacy and confidentiality issues and options for withdraw.⁴²

Withdrawal of participants' consent is an important issue. According to various regulations, return or destruction of samples cannot be enforced because the anonymization of samples accommodates ethical issues.⁴³ The European Society of Human Genetics suggests that unlinked/anonymized samples guarantee absolute confidentiality and that these particular samples can be used for new research purposes without the need of re-consenting.³⁹ Moreover, the International Bioethics Committee (UNESCO) insists that consent to research can be withdrawn by the donor, unless such data are irretrievably unlinked to the individual and that data and biological samples must be dealt in accordance with the wishes of the donor.⁴⁴

Sometimes the initial research protocol needs to be changed after biospecimens are collected. Technological advances may lead to a broadened range of initially-intended research (e.g. genomic analysis), which could not have been predicted in advance. For the above mentioned reasons a "*broad consent*" covering all future aspects of the participant's biomaterial is usually employed.⁴⁴ The European Council has already adopted the position that broad consent to future research use is acceptable, however this is not always favorably viewed by the public.⁴⁵ An alternative solution might be the "*dynamic consent*", which is allowing the participant to give consent on an ongoing basis over time, perhaps with the help of an internet-based digital platform.

Furthermore, biobank samples and associated data may be passed to researchers either directly or indirectly affiliated to the biobank and this transfer raises legal and ethical issues about the ownership of the collected biomaterial. The recipients of samples should use them solely for the purposes that are included in the consent signed by donors and privacy risks should be eliminated.^{35,36} A variety of IT methods has been proposed to address this issue. DataSCHIELD is an example, allowing simultaneous analysis -at the individual level- of data originating from distant operations.^{46,47} The purposes of the use of samples by collaborating parties should not compromise the work of the original biobank and the distant operator ought to comply with quality assurance standards that are equivalent to those of the

original institution who is in charge of the biobank.³⁸

Quality assessment of biosamples and biobanks

Human biospecimens form the basis of biobanks. For this reason, it is of paramount importance not only to collect a sufficient number of biosamples but also to achieve high quantity standards associated with efficient sampling, storage and analysis of biological specimens. High-quality samples are generally considered those with the closest resemblance to the biospecimen prior to its removal from the human donor.⁴⁸ More than 300,000,000 specimens have been stored in US biobanks.⁴⁹ However, researchers often have difficulties finding samples of adequate quality and in many cases have been obliged to change or limit their research goals. This not only undermines their research initiative, but also renders their work inadequate and ineffective.

The increasingly recognized variation among biospecimens has led to the development of general guidelines concerning the collection, processing and storage of biological samples. Some protocols that are publicly available include the ISBER (International Society for Biological and Environmental Repositories), NCI (National Cancer Institute), IARC (International Agency For Research on Cancer), OECD (Organization for Economic Co-operation and Development), ABN (Australasian Biospecimen Network) and CTRNet (Canadian Tumor Repository Network).⁵⁰ The intended end use of biospecimens and the processing methods to which they are subjected to, also determine the methods that are being used during their collection.

The importance of elapsed time between collection and processing of specimens depends on the research application. Generally, processing of specimens should be carried out as rapidly as possible. However, a variety of factors may affect the samples quality and these factors cannot always be eliminated.⁵ These are broadly classified in main two categories: a) “*pre-analytical factors*” that affect the sample integrity prior to its removal from the human participant, up to the point when it is used for testing (e.g. surgical procedures, anesthesia medication and duration, room temperature, type and time of fixation, rate of freezing etc) and b) “*analytical factors*” that affect the performance of a particular testing procedure.^{9,31}

For these reasons, a quality management system (QMS) that includes standardized quality assurance/quality control (QA/QC) policies is essential for the collection, processing, management and distribution of biospecimens (9). Quality Assurance (QA) is a general approach to management activities that focuses on operational improvements in all aspects of activities, in order to ensure that a procedure or product is of the per-defined required quality. Quality Control (QC) is a system of technical activities that measures the attributes and performance of a process or item, against defined standards to verify that the stated requirements are fully met.⁵¹ Infrastructure and equipment maintenance, staff training, safety and contingency plans and assessment of specimen quality should be consolidated within the QC system. It is the responsibility of trained staff to ensure conformation to regulatory demands and policies, as well as to review and accredit handling, processing and storage practices of specimens.⁵²

The first quality standard specific to biobanks was produced by AFNOR (Association Française de Normalisation) in 2008. This regards the NF S 96-9000 standard, which is based upon the ISO 9001:2000 and the OECD (Organization for Economic Co-operation and Development) recommendations.⁵⁰ ISO 9001:2000 is pertinent to several aspects of biobank management and it is being increasingly embraced by biobanks across Europe. Large biobanks invest a great deal in advance technologies that support better biomaterial collection and preservation. Replacing manual procedures by automated storage and retrieval systems, freezers capable of reaching -200°C for complete blockage of enzyme function, techniques that slow hydrolysis and oxidation, modification of formalin fixation and biomarkers capable for quality assurance are some of the methods used to provide excellent quality storage of biomaterials.⁴⁸

Data management-Bioinformatics

Informatics systems permit the undisrupted everyday activity of researchers, the adaptation to future needs such as new processing methods or new equipment technology and support in all aspects of biomaterial operations that are essential for the success of a biobank project.⁵³ Biobanks are required to protect personal information and data related to specimens. This requires the implementation of secured, assembled bioinformatics systems.

Data stored in the repository should be protected with the same rigidity as patient clinical files and personal identifiers should be coded.⁵⁴ A record management system that allows data records concurrently with the implementation of all stages of specimen handling is essential and full traceability of records is mandatory. Examples of such systems are the LIMS (Laboratory Information Management System) or the caBIG (NCI Center for Bioinformatics).¹⁰ Data security systems have to be sufficient in ensuring confidentiality and security of stored records, whereas regular audits should be carried out to ensure operational competence.⁴⁷

Interoperability is another major parameter for the

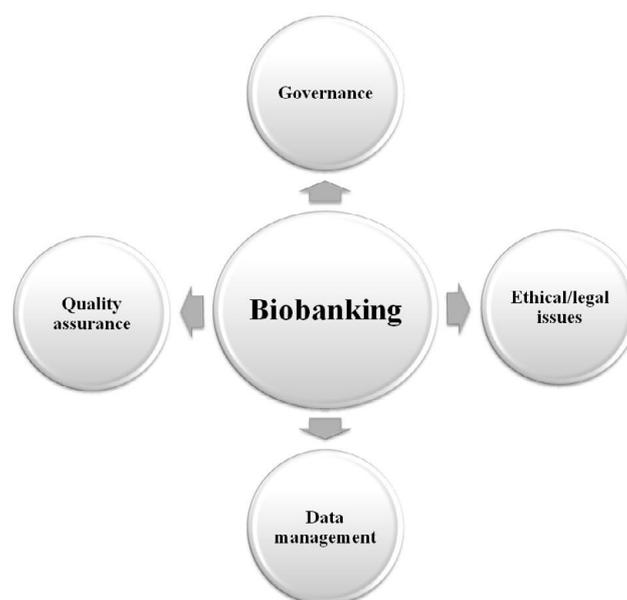


Figure 1: Key concepts of modern biobank development.

coordination of different biobanks, data exchange between different research centers and the development of biobank networks. Communication of information is a pre-requisite for international cooperation.¹⁸ Efficient server dynamics with security credentials must be provided by the administrator to all registered users.⁵⁵ Effectively, an IT facility for the management of input and output of biospecimens must be available in accordance with all ethical, legislative and quality issues discussed in the previous sections (Figure 1).

Conclusion

Human biobanks hold the key to new scientific approaches, such as multi-center and multi-disciplinary translational research. Specimens collected in the context of biobanking may contribute to the discovery of new genes predisposing to genetic diseases, as well as to the systematic analysis of complex pathogenic mechanisms. In Europe, connection of biobanks in the context of the BBMRI initiative facilitates the flow of data and biological samples across laboratories. Likewise, biobanks seem to lead the way of personalized medicine in the scientific world across the globe. For this road to be fruitful, however, several technical, social, ethical and legal issues have to be resolved. Overcoming these issues, is mandatory for biobanks' successes and the advancement of medical research in the 21st century.

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