Pierre Hainaut · Jim Vaught
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Biobanking of Human Biospecimens

Principles and Practice

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20 Years of Biobanking: Dawning of a New Era

Keywords Biobanking • Biorepository • Biospecimen • Biospecimen research • Quality management • Cryopreservation

In 2009, Time Magazine included "Biobanks" among "10 ideas changing the world right now." The term "biobank" is also variously termed biorepository, biospecimen resource, and biological resource center. For the purposes of this volume biobank refers to the collection of human biospecimens for basic, translational and clinical research, and the practices necessary to accomplish such research with biospecimens and data of consistent quality. However, even the use of the term "biobank" elicits a variety of opinions as demonstrated by Hewitt and Watson in a recent survey [1].

It comes as a surprise that a field of rather technical and organizational nature has attained such a level of recognition in the media. This success heralds the huge development of biobanks and biobanking practice over the past 20 years. From a side-activity fuelling research by pathologists, geneticists, microbiologist, or specialists of species preservation, biobanking has become the cornerstone for the mapping of the human genome, for delivering personalized medicine in the clinics and for identifying risk factors of diseases around the world. It is now estimated that several billions of biological specimens are maintained in storage in biobanks worldwide. Given current estimates on the average cost of acquisition, storage, and processing of one biospecimen, this huge number represents the value of the GNP of a small European state—or of a large multinational company.

A striking parallel may be drawn between the expansion of biobanking and the Big Data revolution that characterizes the first decades of the twenty-first century. The "four V's" of Big Data also apply to Biobanking: volume (scale and number of specimens); velocity (collection and analysis of streams of specimens within very strict time constraints); variety (different types of specimens); and veracity (uncertainty on the preservation status of biomolecules, cells, and tissues within a specimen). Like Big Data, large-scale biobanking raises new challenges in terms of ethics and respect of the individual's rights. Like Big Data, it also entails major

infrastructure and management costs and raises concerns about the long-term control and accountability of these infrastructures. With the rapid development of very high-throughput methods to extract large-scale molecular information from smaller and smaller biospecimens, biobanking should be seen as becoming entirely interoperable with informatics and data processing, redefining the biological information contained in stored biospecimens as "digital information in waiting."

This volume, *Biobanking of Human Biospecimens*, is an effort to provide an up-to-date reference for biobanking professionals concerning the technical and ethical, legal, and social issues facing this burgeoning field today.

The title of this introductory chapter, *20 Years of Biobanking*, was chosen because it was during approximately the mid-1990s that researchers began to think of collections of biospecimens as critical resources for their projects, which needed to be collected, processed, and stored in a consistent manner. The sequencing of the human genome in 2001 was the biggest impetus for this culture change. With the possibility to generate huge streams of biological data using highly reliable industrial instruments, the pressure for scientific accuracy shifted from the analytic phase in itself to the pre-analytic phase, during which biological resources are collected, annotated, stored, and prepared before being processed in high-throughput instruments. In the late 1990s, specialists in the USA, Europe, Australia, and Japan started to compare and evaluate their biobanking practice, leading to the development in the following decade of evidence-based standards that are now continuously updated and universally recommended (if not always strictly implemented) as "best practice" for biobanking. In part, this general change in attitude resulted from the realization that research collaborations and analyses of clinical samples were suffering from a lack of consistent quality of the biospecimens and associated data [2]. It has been known for many years that, for example, misidentified cell lines lead to many spurious results and erroneous publications. Biospecimen research has been prone to similar problems during the history of biobanking, but it has only been during the last 20 years or so that a concerted effort has been made to develop best practices and otherwise "professionalize" and recognize biobanking and biospecimen research as scientific endeavors in their own right [3].

The long history of biobanking's origins is generally recognized to have begun with collections developed by pathologists for diagnostic purposes [4]. Pathology departments at present still represent a major source of biospecimens (e.g., formalin-fixed or frozen tissue samples), but over the past two decades, the emphasis of molecular pathology has shifted towards cryopreservation of tissue samples to support the development of translational research programs and clinical research into precision (or personalized) medicine approaches to treatment [5]. As translational research and precision medicine have evolved, biospecimens are now recognized as critical resources not only for research but also for healthcare. Today, a number of standard treatment protocols are dependent upon the identification of DNA or RNA biomarkers, requiring the collection, storage, and pre-analytical processing of biological samples managed according to best practices with strong quality management programs [6].

The issues and challenges that apply to pathology samples also apply to other major research areas where biospecimens play a major role, such as basic research, clinical trials, and epidemiological studies. Many researchers have recognized that the quality of their experimental data depends on the quality of reagents and biospecimens. In their own laboratories and clinics, they have made concerted efforts to understand the pre-analytical variables which may affect their analyses and have taken steps to control such variability. However, the publication and wide dissemination of issues related to pre-analytical variables affecting biospecimen quality have not occurred consistently [2, 7]. During these past 20 years the situation has improved through efforts to develop the field of "biospecimen science" and highlight methods studies to discover and publish findings which will result in an overall improvement of biospecimen quality and consistency of collection, processing, and storage practices [8]. The development of biospecimen science has led to a paradigm shift in biobanking, from experience-based to evidence-based practices. In the past, biobanking protocols were merely developed based on consensus on what was perceived to be the most sensible course of action. Today, the emphasis has shifted towards "biomarkers of quality," providing rigorous and measurable indicators to support the qualification of a biospecimen for a specific type of analysis.

These developments in the professionalization of biobanking over the past 20 years can generally be divided into the following categories: (1) development of best practices; (2) emergence of biospecimen science; (3) more widespread publication of biospecimen science studies and evidence-based practices; and (4) the importance of overarching issues such as ethical, legal, and social issues, quality management, and information technology.

The book will be published in two volumes. In this volume, we have selected 13 chapters which address a variety of biobanking topics important to the collection and maintenance of high-quality biospecimens, as well as some of the ethical and regulatory issues which are equally important to the successful conduct of research projects involving human samples and data.

Chapter 1 (Hubel) addresses the principles of cryopreservation, which are the basis for many of the procedures used to properly stabilize samples for analysis. Chapters 2 and 4 (Grizzle, Betsou) provide an overview of the important aspects of quality management and biosafety/biosecurity, which are among the overarching issues that all biobanks need to implement as best practices. Chapter 5 (Betsou) outlines one of the special implementations of a biobank, as a producer of reference materials.

Chapter 3 addresses the special topic of the economics of biobanking. This has traditionally been a neglected aspect of biobanking. In the past 20 years, biobanking has mainly developed through investment into new infrastructure and facilities. The challenge today is to develop an economic model to make these facilities and their operation sustainable with the constraints of restricted budgets. Thus, it has become increasingly important for biobanks to develop business plans and approaches to long-term sustainability.

Several chapters address issues related to the increasingly global nature of biobanking. Chapter 6 (Zawati) provides insights into one of the most important ethical and societal challenges in international biobanking, the balance between personal

autonomy and reciprocity. Chapters 7, 8, and 9 (Hewitt, Vuorio, and Tasse) describe biobanking networks from several perspectives in Europe and elsewhere. The European Union project Biobanking and Biomolecular Research Infrastructure (BBMRI, Chap. 8) [9, 10] in particular is an important initiative that aims to harmonize biobanking practices in Europe and internationally.

Chapters 10, 11, and 12 (Lawlor, Gan, Vaught) provide additional descriptions of biobanking in various international settings. Chapter 10 discusses biobanking in low resource settings, where the full implementation of best practices may be hampered by limited access to a full array of materials, equipment, services, and trained personnel. Chapters 11 and 12 describe biobanking in China and Africa, the latter being an example of a large region where biobanking is conducted in both low and high resource contexts. Over the past 20 years, China has emerged as a powerhouse for biobanking, with a vast biobanking infrastructure development program.

Finally, in Chap. 13 (Comizzoli), special issues related to "Cryobanking biomaterials from wild animal species to conserve genes and biodiversity" are addressed, and although this is the only chapter not specific to human biobanking, this raises issues that are relevant to all biobanking initiatives.

Volume 2, to be published later this year, will complement this first release by addressing issues such as international biobanks, the design of biobanking facilities, standards and governance for biobanks, biobanking seen from the pathologist's or the patient's perspectives, education and training programs, and the future of biobanking.

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Contents

Principles of Cryopreservation

Allison Hubel and Amy P.N. Skubitz

Abstract Biospecimens are important reagents that are used to diagnose disease, monitor response to treatment and help in the development and testing of new therapies to treat human disease. In order to provide these critical functions, biospecimens need to maintain their requisite biological properties between the time that they are collected and when they are used. It is common for biospecimens to be frozen to preserve those critical biological properties. The purpose of this chapter is to describe our scientific understanding behind the freezing, storage and thawing processes that take place during cryopreservation and the manner by which these processes can preserve or damage the sample. Practical hints for applying scientific principles to daily biobanking practice are also included.

Keywords Biospecimens • Cryopreservation • Cooling rate • Warming rate • Storage temperature

1 Introduction

Biospecimens include tissues, cells and bodily fluids (and their constituent macromolecules). It is common for biospecimens to be collected for use at a later time and different location. The U.S. National Cancer Institute (NCI) of the National Institutes of Health (NIH) has developed the "NCI Best Practices for Biospecimen Resources" (http://biospecimens.cancer.gov/bestpractices) which is based on extensive research and expert input. Similarly, the International Society for Biological and Environmental Repositories (ISBER) has developed their "Best practices for

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repositories: collection, storage, retrieval, and distribution of biological materials for research" [1]. Both of these documents provide practical advice on the operational, technical, ethical, legal and policy best practices for repositories that collect biospecimens. In this chapter, we will discuss the science behind the cryopreservation techniques that are recommended in these two best practice documents.

It is imperative that the biological properties of each biospecimen are preserved during processing, transport and storage. In order to inhibit degradation, the most common method used to preserve biospecimens is cryopreservation, whereby biospecimens are frozen and stored at low temperatures [2]. Chemical fixation [2], plastination [3], drying [4], lyophilization [5], ionic liquids [6] and confinement [7] can also be used to stabilize samples prior to downstream use in future analyses. The focus of this chapter will be on the core scientific principles associated with cryopreservation of biospecimens.

On a molecular level, freezing inhibits degradation by reducing the mobility of molecules that participate in the degradation process: proteinases, carbohydrases, lipases, DNases, RNases, and water. The mobility and activity of these degradative molecules and water vary with temperature during freezing, and our understanding of that behavior frames the scientific principles of preservation. Thermodynamic principles guide the behavior of water at low temperature; nucleation, crystal growth and solidification reflect the influence of interfacial free energy, Gibbs free energy and thermodynamic equilibrium [8]. Proteins that degrade molecules present in solution also behave according to thermodynamic principles; their activity and physical conformation vary with temperature and interfacial interactions, specifically interfacial interactions with ice, influencing that activity and conformation [9–11]. This chapter will describe current theories based on core thermodynamic principles and the scientific evidence that supports them. More thorough details of the core thermodynamic principles behind preservation can be found elsewhere [8, 10, 12]. In addition, this chapter includes practical hints for translating scientific principles into daily best practices for biobanking.

2 Acquisition and Processing (Preanalytical Variables)

Not surprisingly, what happens before a biospecimen is frozen can influence the response of the biospecimen to the stresses of freezing and thawing. For the purpose of this chapter, we will define 'preanalytical variables' for a biospecimen as collection and processing techniques that occur before the freezing process or after thawing. The container used for collection and/or processing is also considered a preanalytical variable. The importance of these processing steps on the quality of the biospecimen post thaw (and therefore the outcome of whatever analytical technique is used) has resulted in the development of a standard method of annotating or describing those processes. ISBER has developed a standardized method to describe all of these steps. Standard PREanalytical codes (SPREC) are used to describe each processing step that has been

determined to be critical to biospecimen quality and can be incorporated into a quality control system for a biobank [13, 14]. More research is needed to develop comprehensive methods to analyze the effect of preanalytical variables on biospecimens, as a recent study has shown that few markers are currently in place to determine the quality of biospecimens that are stored in biorepositories [15]. In fact, recommendations have been put forth by members of ISBER and NIH/NCI's Office of Biorepositories and Biospecimen Research that call for authors of scientific manuscripts to report the preanalytical factors that were used during the collection and processing of biospecimens; they coined the term, "Biospecimen Reporting and Improved Study Quality" recommendations (BRISQ) [16].

2.1 Fluid Samples

Fluid biospecimens (e.g. whole blood, plasma, serum, urine, bronchoalvelolar lavage, saliva, ascites, tear fluid, and seminal fluid) are complex and commonly contain cells, proteins, lipids, and metabolites that can serve as biomarkers. In terms of preanalytical processes, several different preanalytical variables have been shown to influence the quality of a fluid biospecimen, including: (i) duration of hold prior to centrifugation, (ii) container for collection, and (iii) the presence of a second centrifugation step, reviewed in [15] among others.

Most studies that have addressed the influence of delay prior to centrifugation on fluid biospecimens have involved the study of whole blood, serum or plasma. Relatively short holding times (~2 h) have been shown to influence proteins measured in whole blood samples. Ayache et al. [17] observed that levels of 37 different factors (principally cytokines) changed significantly within 2 h after venipuncture. Furthermore, the study determined that these changes resulted from production of cytokines by the neutrophils in the whole blood sample responding to the stress of collection and short-term storage (at 4 °C or room temperature). Banks et al. [18] examined the stability of low molecular weight serum proteins by SELDI-mass spectrometry and determined that significant changes occurred between 30–60 min after collection and then remained constant for up to 4 h post collection. Ostroff et al. [19] determined that the majority of the 498 proteins examined in an aptamer-based proteomic array were stable if the sample was centrifuged within 2 h of venipuncture and frozen within 2 h after centrifugation. Holding temperatures also influence protein stability. Significant protein losses were observed by mass spectrometry when sera samples were kept at room temperature for more than 4 h or kept at 4 °C for 24 h [20]. Recently, Kalmage et al. [21] analyzed blood samples that had been processed with differences in microclotting, prolonged processing times at different temperatures, hemolysis, and contamination with the buffy coat layer. They also analyzed plasma samples that had been incubated at different temperatures for up to 16 h [21]. By mass spectrometry-based metabolite profiling, they detected metabolites that were sensitive to these preanalytical variations, which may serve to control for sample quality [21].

When collecting a blood sample, the container is also a critical preanalytical variable. This preanalytical variable has two components: (i) the composition of the container, and (ii) any additives that are preloaded into the container by the manufacturer. The most common example of this is a tube used for blood collection; both the tube and its contents (typically anticoagulants or stabilizing agents for nucleic acids) may influence the analysis of biomarkers in the blood sample. The composition of the tube has been shown to influence analysis of proteins, hormones and other classes of biomarkers using a variety of analytical techniques [22–24]. Stabilizing agents can also influence biomarker recovery. For example, ethylenediaminetetraacetic acid (EDTA) is necessary for stabilization of folates and vitamins (reviewed in [25]).

2.2 Solid Biospecimens

The preanalytical variables for tissue are slightly different than those of fluid biospecimens as the molecular mechanism for changes in the biospecimen after removal from the body is different. The ischemic time and temperature of ischemia (warm or cold) are critical preanalytical variables for tissue biospecimens. The loss of blood supply to a tissue produces a cascade of events that has been well studied in fields such as organ preservation, trauma, and stroke [reviewed in [26]]. Studies have also found that a loss of blood supply to the tissue biospecimen results in a rapid loss of biomarkers [reviewed in [2]], whether detected using molecular techniques or using standard immunohistochemistry. Recent studies by Meric-Bernstam et al. [27] have shown that breast cancer biospecimens that are collected as core-needle biopsies differ in PI3K pathway markers when compared to biospecimens that are collected post-surgery. Their studies suggest a potential loss of phosphorylation during surgical manipulation or with cold ischemia of surgical specimens [27].

3 Freezing

3.1 Principles

As described above, most biospecimens are complex mixtures and may contain cells, water, ions, lipids, carbohydrates and proteins. The principles of thermodynamics require that these complex mixtures do not freeze at a single temperature, but rather over a range of temperatures [12, 28]. The freezing behavior for these systems follows what has been described as a phase diagram [12]. Specifically, the fraction of water that has been solidified and the corresponding concentration of the unfrozen fraction of solution can be determined based on temperature, for a given initial concentration and pressure [29–33]. Cell membranes also express changes in conformation (e.g. phase transitions) during cooling and can be described by phase diagrams as well [34].

Unlike most materials, water can undercool significantly below its equilibrium freezing temperature [35]. Specifically, pure water has been measured to freeze at temperatures ranging from 0 °C to −40 °C [36]. The onset of freezing is called nucleation and occurs when water molecules form stable ice crystals in the sample. In controlled-rate freezing of specimens, the temperature at which ice is formed may be controlled through the use of a seeding step, whereby one part of the freezing protocol is programmed into the freezer. In samples that are passively frozen (e.g. placed in a subfreezing environment like a −80 °C mechanical freezer), the temperature at which ice forms is not controlled and will vary from sample to sample based on sample volume, heat transfer and the stochastic nature of the nucleation process. It is not unusual for fluid biospecimens that are frozen to form ice at temperatures ranging from −5 °C to −15 °C.

After nucleation occurs, water is removed from the sample in the form of a solid ice crystal. Solutes (e.g. proteins and salts) are not incorporated into the solid ice crystal. This results in a partitioning of the sample into a solid component and the unfrozen liquid component whose solute concentration increases as the temperature of the sample decreases. Cells, proteins, lipids and other components of the biospecimen are sequestered in the gap of unfrozen liquid between adjacent ice crystals [37, 38]. When much of the water has been removed in the form of ice, the solutes in the remaining unfrozen liquid become highly concentrated [39] and the molecules, cells and tissues are subjected to these very high solute concentrations [40]. Within the small gap between adjacent ice crystals, the distribution of molecules may not be uniform. Spectroscopic studies of protein solutions have demonstrated that the distribution of protein was not uniform and proteins aggregated near the ice/water interface in gaps as small as 1 μm [10].

Water in the form of ice continues to be removed from the solution until the sample is fully solidified. The binary phase diagram of NaCl-water is often used as a model of the freezing behavior of biological systems in the absence of cryoprotective agents [12]. As the sample cools, water is removed in the form of ice and the remaining unfrozen solution becomes higher in concentration of NaCl until the sample achieves the eutectic temperature at which ice and hydrated salts precipitate out from the solution. Alternatively, the sample may vitrify (form an amorphous phase) at the glass transition temperature, T_g. For an isotonic saline solution, the eutectic temperature occurs at −21.2 °C. Angell [41] reported that isotonic saline solutions (0.154 M) cannot vitrify under "normal" cooling procedures. In contrast, a commonly used solution for cell preservation, 10% (w/w) dimethylsulfoxide (DMSO) solution, does not form a eutectic (the point where the solidus and liquidus temperatures meet) when frozen, but will completely solidify at roughly −133 °C [42]. Below the glass transition temperature, the mobility of molecules within the sample is reduced due to an increased viscosity of 10^{13} Pa-s.

One common method of describing the freezing process is in terms of the cooling rate during freezing. The survival of biological cells that are frozen is strongly influenced by the cooling rate [43]. It is common for plots of cell survival as a function of cooling rate to take the form of an inverted "U." Optimum survival happens at an intermediate cooling rate (or narrow range of cooling rates). Cell survival at cooling rates higher than the optimum declines rapidly with increasing cooling rates

and survival decreases at cooling rates below the optimum cooling rate. The optimum cooling rate for a cell type will vary with both cell type and composition of the freezing medium (reviewed in [44]).

Freezing induces several types of stresses on proteins. For example, reducing the temperature can lead to cold denaturation of proteins (e.g. protein unfolding) [9]. In addition, proteins have been observed to interact with the ice-liquid interface, resulting in unfolding and aggregation [9–11, 45–47]. Freezing may also cause shifts in pH; e.g. low pH environments produced during freezing can may cause proteins to aggregate [11, 48]. The recovery of proteins from a sample varies with the cooling rate imposed upon the sample. Unlike cells, the dependence of protein recovery on the cooling rate varies with the protein. Cao et al. [49] observed a decreasing recovery of lactate dehydrogenase with increasing cooling rate. In contrast, Kueltzo et al. [11] observed an increase in recovery for immunoglobulin frozen rapidly versus slowly. Nonetheless, it is clear that the freezing process and the rate at which it takes place can influence the conformation of the protein, its tendency to aggregate, and ultimately its recovery.

Unlike cells, fluid biospecimens are not typically frozen in controlled rate freezers, but passively in mechanical freezers. The highest cooling rate that a sample can achieve when placed in an −80 °C freezer is 5–7 °C/min [50]. A variety of factors will influence the actual cooling rate of the sample during freezing. First, the more samples that are already in the freezer will reduce the heat transfer from the sample and therefore decrease the cooling rate. Secondly, orientation of the sample (specifically, whether the sample is directly in contact with the sides of the freezer) will influence the cooling rate that the sample experiences. These factors imply that samples placed in the freezer on different days will probably experience different cooling rates and these differences may result in sample-to-sample variability.

3.2 Putting Principles into Practice

The cooling rate and freezing process is so important to the post thaw viability of cells, that it is common for cells that are to be used therapeutically to be equipped with temperature measurement sensors (typically thermocouples) to measure temperature as a function of time for every freezing run. This temperature history becomes a part of the process record for the product. It is not expensive or difficult to equip samples with instruments and measure temperature as a function of time during freezing. For high value biospecimens, it may be helpful to conduct such measurements for each sample that is frozen; or for a limited number of samples in order to determine the actual cooling rate and its consistency from sample-to-sample. The most common method of achieving a consistent cooling rate for passive freezing is to use a mechanical freezer whose sole purpose is freezing; the samples are positioned the same from run-to-run and transferred to a storage unit after completion of the freezing process.

4 Storage

4.1 Principles

After completion of the freezing process, samples that are frozen using controlled rate freezers are transferred to a storage unit (typically liquid nitrogen). Other samples may remain in the unit in which they are frozen. Currently, commercially available storage units come in a variety of storage temperatures (e.g. −20 °C, −80 °C, −150 °C, liquid nitrogen vapor or liquid). Since these biospecimens may be stored for extended periods of time, the selection of the proper storage temperature is very important [2].

As described in the Introduction, samples are frozen to inhibit degradation of the sample (i.e. retain its critical biological properties). Freezing inhibits degradation by reducing the molecular mobility of water and therefore its ability to participate in chemical reactions that degrade biological systems. Therefore, samples should be stored at low temperatures that ensure that the sample will remain solidified; a sample that is not fully solidified/vitrified will most likely change over time in storage. The temperature at which a sample is fully solidified is typically determined from the phase diagram of the solution in which it is frozen. Unfortunately, phase diagrams have been developed for only a limited number of solutions [12, 51].

In addition to reducing the mobility of water and therefore its ability to participate in reactions that can degrade the sample, freezing reduces the activity of biological molecules. All biospecimens contain degradative molecules, which may include: lipases, carbohydrases, proteases and nucleases. Many of these degradative molecules can act as biomarkers. For example, proteases such as matrix metalloproteinases can act as both biomarkers as well as to degrade other protein biomarkers in a sample [52]. In addition, enzyme activity is protein-specific and will vary with temperature [53]. For example, temperature has a strong influence on protein dynamics; reduced temperatures result in reduced protein dynamics/activity. The dependence of protein activity with temperature follows an Arrhenius relationship [54], whereby the rate constant, k, of a chemical reaction is dependent upon the absolute temperature T:

$$k = A \times e^{-Ea/(R \cdot T)}.$$

with the pre-exponential factor, A, the activation energy, Ea, and the universal gas constant, R. Therefore, low temperatures result in a low rate constant, k, of chemical reactions.

Proper storage temperatures should be selected below the threshold temperature for activity of the protein. Distinct changes have been observed in the dynamic properties of different proteins near −53 °C [55–58]. For example, when the temperature-dependent behavior of ribonuclease A (RNA A) was studied by Rasmussen et al. [59], it was determined that the substrate failed to bind RNA A at 215 K (−58 °C). Similar results were observed by Tilton et al. [60] in which RNA

A was observed to change behavior at 180–200 K (−93 °C to −73 °C). In contrast, More and colleagues observed activity of β-glucosidase at temperatures as low as 203 K (70 °C).

After being placed in storage, biospecimens may be subjected to temperature excursions resulting principally from users accessing the storage unit to remove or store other samples (e.g. opening the door of a mechanical freezer and removing samples or lifting a storage rack out of liquid nitrogen and removing a sample). Transient warming and cooling of a sample in storage may result in the sample passing through specific phase transitions (e.g. the glass transition temperature or even repeatedly thawing and freezing, depending upon the extent of the temperature excursions). A limited number of studies have examined the role of cyclical temperature excursions on post thaw recovery. Cosentino et al. [61] cycled samples of peripheral blood mononuclear cells through different temperature excursions and observed higher levels of apoptosis markers for the cells that had been cycled versus controls that had not.

4.2 Putting Principles into Practice

The scientific principles described above suggest that biospecimens should be stored at temperatures where the sample is fully frozen. The simple reality is that phase diagrams have not been developed for the wide array of solutions that are frozen (plasma, serum, urine, bronchoalveolar lavage, etc). Similarly, the functional activity of all proteins at low temperatures have not been measured. For example, plasma contains >15,000 proteins [62] and the dynamics of all of these proteins at low temperatures has not been determined. Therefore, it is not easy to select a storage temperature based on scientific principles alone. A conservative approach involves storing samples at the lowest possible temperature (i.e. liquid nitrogen). An alternative is to use quality control/quality assurance programs to select storage temperatures. For example, a small number of biospecimens could be collected for quality control testing (i.e. not for distribution). These samples could be monitored pre-freeze, post-freeze, and as a function of time in storage for the presence of the biomarkers of interest. Degradation of the biomarkers with time in storage suggests that the specimen is not being stored properly and should be stored at a lower temperature to further reduce the mobility of water and the activity of degradative molecules. A summary of studies that have examined the influence of storage temperature on the stability of specific biomarkers is given in Table 1 and was taken from [126] with newly published studies included.

The influence of temperature variations during storage on biospecimen quality suggests that repositories should be accessed as infrequently as possible. For example, requests for biospecimens could be pooled and the repository accessed only once per day to retrieve samples. Furthermore, staff members who are responsible for retrieving biospecimens should be trained on the importance of limiting the temperature excursions that stored sample experience when the freezer is opened.

Table 1 Compilation of studies describing the stability of specific biomarkers for biospecimens (biofluids, cells, tissues) as a function of storage temperature/duration

Biospecimen	Duration	Storage temperature	Tracked analyte	Stability	Reference
Fluid biospecimens					
Biological fluids	60 min	RT, −80 °C, −120 °C	Creatinine	M	[63]
Blood	2–96 h	21 °C, −80 °C	C-reactive protein, retinol, ferritin, folic acid, fatty acids	M	[64]
Blood	10 min to 8 h	1.5 °C to −4.3 °C	Heparin	S	[65]
Blood	120 h	30 °C, 4 °C, −20 °C	Hormones in plasma and serum	M	[66]
Blood	4, 8, 24 h	35 °C, 25 °C, 15 °C	Thirty-five biochemical analytes	M	[67]
Blood	24 h	38 °C, 30 °C, 22 °C, 3 °C	Albumin, calcium, cholesterol, chloride, creatinine, glucose, sodium, potassium, inorganic phosphorus, bilirubin, total protein, uric acid, urea nitrogen, total CO_2, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, creatine kinase, lactate dehydrogenase	M	[68]
Blood	1 year	20 to −196 °C	Hemoglobin	M	[69]
Blood	8, 15, 24, 72 h	RT, 4 °C	Factor VIII	M	[70]
Blood	0.25, 0.5, 1, 2, 4, 24 h	RT, 4 °C	Six human recombinant cytokines [tumor necrosis factor , interferon-alpha (IFN-alpha), IFN-gamma, interleukin-1 alpha (IL-1 alpha), IL-1 beta, and IL-6]	M	[71]
Blood, plasma	24 h	−80 °C	Cell-free DNA	N	[72]
Blood, plasma	80 days	−70 °C	Ascorbic acid	N	[73]
Blood, plasma	14 days	22 °C, 4 °C, −6 °C	Vitamin B_{12}, folate	M	[74]
Blood, plasma	3–48 months	−20 °C	Vitamin A, B_1, B_2, B_6, B_{12}, E, niacin	M	[75]
Blood, plasma	6 months	−20 °C, −80 °C, −150 °C	Polyunsaturated fats	M	[76]

(continued)

Table 1 (continued)

Biospecimen	Duration	Storage temperature	Tracked analyte	Stability	Reference
Blood, serum	1, 3–5 months	−20 °C	Anti-dengue IgM and IgG antibodies	N	[77]
Blood, serum	72 h	RT	25(OH)-vitamin D_3	N	[78]
Plasma	1 year	−80 °C	Matrix metalloproteinase-9	N	[79]
Plasma	2 year	−20 °C, −80 °C	Triglyceride, high-density lipoprotein, cholesterol	N	[80]
Plasma	37 months	−38 °C to −42 °C	Coagulation factors FV, FVIII:C and FXI; major inhibitor antithrombin III (AT III)	S	[81]
Plasma	15 min to 8 h	23 °C, 4 °C, −80 °C, −196 °C	Lithium-heparin, sodium-citrate	M	[82]
Plasma	24 months	−24 °C, −74 °C	Clotting assays for factors II, V, VII, VIII, IX, X, XI and XII	M	[83]
Plasma and urine	1 year	−20 °C, 4 °C, −20 °C, −70 °C	Catecholamines (CA)	M	[84]
Serum	5 years	−20 °C	Matrix metalloproteinase-7	M	[85]
Serum	18 days	−20 °C, −70 °C	Folate	N	[86]
Serum	7 days	Refrigerated	Vitamin B12, folate	M	[87]
Serum	7 days	RT, 4 °C, −20 °C, −70 °C	Free prostate-specific antigen	M	[88]
Serum	1–24 h	37 °C, RT, 4 °C, −80 °C	ACT-PSA	M	[89]
Serum	7 days	RT, 4 °C, −20 °C	PSA, fPSA, cPSA, tPSA	M	[90]
Serum	1 week, 3 months	4 °C, −20 °C, −80 °C	Serum apo E	M	[91]
Serum	10 days, 3 months	4 °C, −20 °C	Lipid, lipoprotein, apolipoprotein	M	[92]
Serum	10 years		Cancer antigens, CA-125 and CA-15-3	N	[93]
Serum fatty acids	12–24 months	−2 °C, −80 °C	Docosapentaenoic acid, docosahexaenoic acid	M	[94]

Serum, plasma	3 years	37 °C, 4 °C, −20 °C, −80 °C, −150 °C	C-telopeptides of type I collagen (CTX)	S	[95]
Serum	0.5–23 years	−25 °C	Thyrotropin, thyroid hormones, and thyroid autoantibodies (TSH, fT4, TPO-Ab, or TG-Ab)	S	[96]
Serum	8–11 years	−80 °C	Thyroid-stimulating hormone (TSH)	N	[97]
Specimens for gastrin	2 weeks	−70 °C	Cholylglycine, cortisol, digoxin, ferritin, follitropin, immunoglobulin E, lutropin, prolactin, thyroxin (also blood-spot thyroxin), triiodothyronine	M	[52]
Urine	3–24 months	−20 °C	Urinary albumin	M	[98]
Urine	160 days	−20 °C, −70 °C	Urinary albumin	S	[99]
Cells					
Bone marrow cells	40–42 months	−85 °C, −140 °C, −190 °C	Cell number and granulocyte-monocyte colony—forming cell (CFU-c)	M	[100]
Bone marrow cells, peripheral blood mononuclear cells (PBMCs)	48 h, 26–78 months	−90 °C	Cell recovery, viability, colony-forming unit-granulocyte macrophage (CFU-GM), clonogenic potential of autologous hematopoietic progenitor cells	M	[101]
Erythrocytes	37 years	−10 °C to −75 °C,	Freeze-thaw-wash recovery, hemolysis, ATP, 2,3-DPG and P50 levels, and 60% of normal RBC K+ levels	S	[102]
Hemopoietic progenitor cells	1–31 months	−80 °C	Cell recovery, viability, colony-forming unit-granulocyte macrophage (CFU-GM),	M	[103]
Hemopoietic stem cells (HSCs)	5–14 years	−196 °C	Viability, colony formation	S	[104]
Hemopoietic stem cells (HSCs)	Weeks	−196 °C moved to −80 °C	Viability, colony formation, apoptosis	N	[105]

(continued)

Table 1 (continued)

Biospecimen	Duration	Storage temperature	Tracked analyte	Stability	Reference
Hemopoietic stem cells (HSCs)	12–24 months	−40 °C, −80 °C, −130 °C	Viability, colony formation	M	[106]
Hemopoietic stem cells (HSCs)	11–19 years	−180 °C	Viability, colony formation	S	[107]
Liver cell spheroids (alginate-encapsulated)	1–12 months	−80 °C, −196 °C	Hepatospecific protein enzyme-linked immunosorbent assay	N	[108]
Peripheral blood progenitor cells (PBPCs)	10–12 months	−140 °C	Nucleated cells count, multilineage colony-forming assay, long-term culture-initiating cell assay and erythroid burst-forming assay	S	[109]
Peripheral blood progenitor cells (PBPCs)	1–2 years	−80 °C, −196 °C	Membrane integrity, colony formation	M	[110]
Peripheral blood progenitor cells (PBPCs)	7 weeks	−80 °C	CD34+, Colony-forming units granulocyte-macrophage (CFU-GM), burst-forming units erythroid (BFU-E)	M	[111]
Peripheral blood progenitor cells (PBPCs)	30 days	−150 °C, −80 °C, −30 °C	Membrane integrity, apoptosis, necrosis	M	[112]
Peripheral blood stem cells (PBSCs)	5 years	−80 °C, −135 °C	Total nucleated cell, cell viability (using acridine orange and propidium iodide), CD34+ cell content, colony-forming unit-granulocyte-macrophage content	M	[113]
Peripheral blood stem cells (PBSCs)	1–61 months	−80 °C	Colony-forming units granulocyte-macrophage (CFU-GM), burst-forming units erythroid (BFU-E)	M	[114]
Platelets	1–10 days	22 °C	A, B, 2H, PlA1, and HLA Class I antigens	M	[115]
Platelets	9 days	−80 °C	Septin 2	M	[116]

Sperm	7 days, 3 months	−70 °C, −196 °C	Motility, morphology	M	[117]
Tissue biospecimens					
Breast tumor	100 days	−20 °C, −196 °C	Specific estrogen receptor	S	[118]
Heart valves	~3 months, 1, 2 years	−80 °C, −135 °C	Tritiated-glycine	M	[119]
Prostatic tissue extracts, plasma	45 days	−20 °C, −90 °C	Creatine kinase	M	[120]
Reproductive tract	2–8 weeks	−196 °C	Estrogen and progestogen receptor	S	[121]
Skin	1–12 months	−196 °C	Chromosome	S	[122]
Breast, colon, liver, lung, ovary, endometrium, cervix	5 days	RT, −70 °C	DNA, RNA	M	[123]
Tumor tissue, tumor cells	1 year	−80 °C	Cell cycle phases	M	[124]
Liver tissue	3 months-10 years (simulated)	−80 °C to −196 °C cycles	Peptides and lipids	M	[125]

Note the notation for the stability of the tracked analyte: *S* stable, *N* non-stable, *M* multiple outcome

5 Warming

5.1 Principles

Prior to use in most clinical and research labs, most biospecimens must be warmed from the cold storage temperature to room temperature. The biospecimen must traverse the same temperature range during thawing as during freezing, but in reverse. The same chemical and physical phenomena observed during freezing are also present during warming. For example, during warming, glasses that form during freezing may devitrify and ice crystals form during thawing. Similarly, small ice crystals formed during freezing may find it energetically favorable to grow during thawing; resulting in what has been described as recrystallization damage [127]. Therefore, the influence of warming on the quality of what has been frozen can be as profound as that of freezing. It is noteworthy that warming starts as soon as the sample is removed from the repository's freezer. Warming of samples in air can be very rapid (~80 °C/min) initially, with warming rates diminishing with increasing temperature; implying that significant thawing events (devitrification and recrystallization) may be taking place rapidly.

A limited number of studies have examined the role of thawing/warming rate on post-thaw function. Cao et al. [49] observed that the activity of lactate dehydrogenase and aldehyde dehydrogenase increased with increasing warming rate (1 and 15 °C/min). The majority of studies on the influence of warming rate have looked at the influence of warming rate on post-thaw viability of cells that have been cryopreserved. In general, rapid warming rates have been shown to result in improved post-thaw viability (reviewed in [44]). However, some studies suggest that warming rates may depend upon the freezing rate, as well as the composition of the freezing solution. For example, mouse embryos that are slowly frozen in 1.5 M DMSO survived when thawed rapidly [128]. In contrast, mouse embryos that are slowly frozen in glycerol exhibited higher rates of post-thaw viability when thawed slowly [129]. These results suggest that the thawing rate plays an important role in post thaw recovery of biospecimens. Due to the complexity in the relationship between thawing rates and recovery, the thawing rates should be validated for biospecimens of high value.

5.2 Putting Principles into Practice

Estimating an average thawing rate is not that difficult. *The average thawing rate is just the temperature difference divided by the time it takes to thaw*. All that is needed is a stopwatch to time the thawing process, the temperature of the storage unit and the melting temperature of your sample. One can measure the time that it takes for the sample to thaw to the point where there is only a small ice crystal in the center and then divide the temperature difference by that time and the result is the thawing

rate. It is also possible to equip a sample with a thermocouple and directly measure the temperature as a function of time for a given method of retrieving a sample from a repository and thawing it. When thawing cells, warming rates >60 °C/min are recommended for cells frozen using conventional techniques.

6 Summary

Biospecimens are commonly collected in one location for later use in another location. Freezing (or cold) is used to stabilize biospecimens and prevent/limit the degradation that can take place. The processing of a sample before it even enters a cold environment can influence its response to freezing. The freezing process (cooling, storage and thawing) can also have an influence on the post-thaw properties of a biospecimen. Since many of the processing steps may affect the quality of the biospecimen post-thaw, it is best to document all preanalytical steps, as recommended by ISBER using SPREC [13]. Finally, it is important to understand that fundamental biological and physical principles drive our understanding of biospecimen preservation. For example, degradation of tissue biospecimens results directly from ischemia injury, a process that has been studied in a variety of diseases/pathologies. The freezing process follows thermodynamic principles of complex mixtures and phase change. These fundamental principles provide the scientific basis for preservation protocols and should inform the daily practices of those who preserve biological specimens as a part of their normal workflow.

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Quality Assurance and Quality Control in Biobanking

Fay Betsou

Abstract An increasing number of biospecimens are being collected in the context of multicenter and international clinical studies and diagnostics. This has revealed the need to optimize management of these biospecimens such that research biorepositories can guarantee that samples distributed to industry or academic researchers are comparable and without institute-dependent intrinsic bias. Acceptance of biological samples and associated data between countries will be facilitated if biobanks can propose validation protocols for their samples and ensure the accuracy of the results obtained from the samples. Certification or accreditation to international standards of the International Standards Organization (ISO) by an independent auditing body provides proof of effective organization, operational consistency and management of the production of "annotated specimens". Subcontracting to testing laboratories, which are themselves accredited to international standards such as ISO 17025 (General Requirements for the Competence of Testing and Calibration Laboratories) or ISO 15189 (Medical Laboratories—Particular Requirements for Quality and Competence), is proof of reliable sample characterization and production of "qualified specimens". Despite the fundamental importance of these standards, compliance remains essentially voluntary to each individual biobank. Development of a system of international technical standards for research biobanks is a critical step, currently being addressed in ISO Technical Committee 276 "Biotechnology".

Keywords Accreditation • Best practices • Certification • ISBER • ISO 9001 • ISO 17025 • ISO Guide 34 • Quality assurance • Quality control • SPREC

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1 Background

Biospecimen collection is fundamental to both diagnostics and clinical studies, and is often performed in an international multicenter context [1]. Results of analyses of biological samples can be influenced by conditions that samples have been exposed to during sampling, processing, and storage prior to usage, known as preanalytical variations [2]. Biobanks need to ensure that samples are interchangeable, without institute-dependent intrinsic bias, offering industry/academia researchers an assurance of the accuracy, reproducibility and comparability of research results. This guarantee may come from sample validation accredited by an external body. A biobank certification/accreditation system requires documentation of the collection of biological samples of known quality, including traceability of sample collection, preparation, aliquoting, storage and retrieval procedures. Assessment of the technical competence and granting of accreditation will give confidence to biobank sample end users, close the current "asymmetric information gap", and facilitate the increasing international/inter-institutional use of research materials from biobanks.

This chapter provides a comprehensive overview of the concepts relevant to quality assurance (QA) and quality control (QC) in the context of biorepositories, presents guidelines and best practices, and certification/accreditation systems currently in use in biobanks, and describes unmet needs and a future strategy.

2 Definitions of Terms

Quality management system (QMS): Organizations control the quality of their activities by implementing a QMS which defines the organization's quality policy and objectives and ensures that these are achieved through Quality Assurance (QA) and Quality Control (QC), the former focusing on the processes through which the product is obtained and the latter on the product. The quality of any product or process can thus be demonstrated by comparison with a quality standard and organizations that can show that they meet the requirements of the standard can gain certification or accreditation.

Quality assurance (QA): This is defined as the part of quality management that focuses on providing confidence that quality requirements will be fulfilled. QA requires systematic monitoring and evaluation of all aspects of a biobank's processes, covering both how the biobank operates as well as the quality of the samples and data held.

Quality control (QC): This is defined by the operational techniques and activities used to verify that a product or service adheres to a defined set of quality criteria.

Best Practice: A management idea asserting that there is a technique, method, process, or activity that is more effective at delivering a particular outcome than any other technique, method, process, or activity. Guidelines or Recommendations are synonyms of Best Practices.

Evidence-based practices: interventions for which there is consistent scientific evidence, either recognized by one or more published articles in scientific journals or provided by on-site experimental work.

Certification: The procedure by which a third party gives written assurance (a certificate) that a product, process or service conforms to specific requirements.

Accreditation: The procedure by which an independent authoritative body gives formal recognition that a body or person is competent to carry out specific tasks. Accreditation requires method validation.

Standards or norms: A format applicable because it is recognized by an official organization or is implemented by a majority of users. It is mandatory for biobanks seeking certification or accreditation to conform to applicable standards.

ISO Certification norm: A norm geared around management which includes feasible Standard Operating Procedures (SOPs) (e.g. ISO/IEC 9001:2015).

ISO Accreditation norm: A norm geared around competence which includes SOPs that are evidence-based and scientifically validated (e.g. ISO 17025:2005).

Preanalytical phase: processes that include, in chronological order, the biological material request, preparation and identification of the origin of the biological materials (donor or environmental site), collection of the primary sample(s), temporary storage, transportation to and within the biobank processing laboratory, processing, isolation of analytes, aliquotting, retrieval, and that end when the biological material is delivered for analysis.

Qualification: process of examination of a biospecimen or a collection of biospecimens, and verification, based on objective analytical evidence, of their suitability for research use, either in a specific disease area or on a specific downstream analytical platform.

Quality stratification: process of examination of a biospecimen or a collection of biospecimens, and their classification, based on objective analytical evidence, into distinct categories, each category corresponding to a specific in vivo biological characteristic (e.g., level of inflammation, % tumour, protein content) or to a specific ex vivo preanalytical condition (e.g., pre-centrifugation conditions).

3 Approaches to Implementing Quality Assurance

A number of guidelines and best practices for collecting biological specimens have been developed, addressing such issues as ethical guidelines for population biobanks or hospital-based biobanks, technical guidelines, IT guidelines, and cost-recovery guidelines. Likewise, certain national and international norms exist, which although not always specific to biobanks, may be applied.

A biobank can be compliant to recognized guidelines, and can also be certified and/or accredited. Compliance to national and/or international guidelines is declared by the biobank itself, but an external audit is not conducted. A self-assessment tool is available from the International Society for Biological and Environmental Repositories (ISBER, http://www.isber.org/?page=SAT), however this remains confidential. Biobanks may be certified by an external body according to a national or international certification norm, providing a guarantee of consistency. For accreditation, a biobank may either be accredited by an external body according to a national or international norm, or can collaborate with an accredited laboratory for testing/characterizing the samples. A description of available best practices and ISO norms used for certification and accreditation in support of biobanking QA follows.

3.1 Best Practices and Recommendations

In 1999, the Organisation for Economic Co-operation and Development (OECD) recommended that national governments 'should support the development of an accreditation system for biobanks based upon scientifically acceptable objective international criteria for quality, expertise and financial stability [3]. While some moves have been made in this direction, accreditation systems established by a body dedicated to the development and dissemination of such standards are lacking. An overview of the guidelines published to date—by the OECD itself, the European Council, the US National Cancer Institute (NCI), and the ISBER—is presented below.

Recommendations were published in 2006 by the Council of Europe which provided Recommendation Rec(2006)4 of the Committee of Ministers to member states for research on biological material of human origin [4]. In 2007, the OECD itself published Best Practice Guidelines for Biological Resource Centers (Paris, France) addressing the certification of repositories containing samples of human and microbial origin to conform to national and/or international standards, with an influence from microbiological material collections [5]. Moreover, the NCI Best Practices for Biospecimen Resources (Bethesda, MD, USA, 2016) were developed for NCI-supported biorepositories which store biological samples of human origin [6]. They focus mainly on management, quality and protection of data associated with the biological material, as well as addressing intellectual property issues.

The most complete best practices for repositories can be found in the ISBER Best Practices for Repositories: Collection, Storage, Retrieval and Distribution of Biological Materials for Research (3rd edition), first published in 2005 with revised editions in 2008 and 2012 [7]. They reflect the collective experience of the ISBER members and provide repository professionals with a comprehensive tool to guide them in a wide range of activities, covering infrastructure, equipment, security, and training. They are applicable to biobanks which manage material of either human or non-human origin, with a focus on the establishment and day-to-day management of a biobank. They take into account regulatory compliance as well as the ethical,

legal and social issues relevant to repositories. Both managerial and technical aspects are covered providing a practical guide to the overall establishment, management and operations of a repository with advice on a wide range of aspects including repository development, facilities and equipment, quality management, cost management, security (pertaining to specimens, handlers and data) and training, material tracking, packing and shipping, sample collection, processing and destruction, and legal issues. These Best Practices are reviewed periodically and revised to reflect advances in research and technology.

3.2 Certification

Biobanks can obtain certification according to the international ISO 9001:2015 (Quality Management Systems Requirements), a flexible and generic management standard that can be applied to any business. It is focused on the implementation of QMS, client satisfaction and continuous improvement, and is highly customer service oriented, with documentation of all complaints, and implementation of corrective and preventive measures. It is applicable to an organization's structure for managing its processes (activities) that transform resource inputs into a product (biological sample or derivative) or service (biostorage) to meet the organization's objectives, such as satisfying the customer's quality requirements or complying with regulations [8]. ISO 9001 certifies that a business has official written procedures and training documentation in the area of customer service, product processing, analysis, packaging, and shipping, as well as for accounting. As long as a repository is consistent in its documented actions, it can remain ISO 9001-certified.

In addition, some countries have developed national standards. In France, the NF S96–900 (Management System of a Biological Resource Center and Quality of Biological Resources of Human or Microbial Origin) were developed on the basis of the ISO 9001 [9]. In addition to the above-mentioned system requirements, it also includes specific technical requirements for biorepositories. In the UK, the National Cancer Research Institute (NCRI) has developed a Biobank standard [10]. In the USA, the College of American Pathologists has also developed a checklist towards biobank accreditation [11].

3.3 Accreditation

While ISO 9001 is a suitable standard for the certification of the QMS of a biobank's activities, ensuring its core processes are consistent, it does not provide assurance of the quality of the technical aspects, the accuracy of any measurements it performs or the professional competence of its staff. This includes qualification of equipment, validation of methods, measurement traceability, use of control and

reference materials, participation in proficiency testing schemes and handling of samples and data—and hence that samples and derived data are fit-for-purpose. To this end, biobanks should also operate in accordance with other international reference documents focused on aspects of competence. The two main references for accreditation are the international ISO 17025:2005 and the ISO 17034:2016.

The ISO 17025:2005 (General Requirements for the Competence of Testing and Calibration Laboratories) is used by biobanks to implement a quality system aimed at improving consistent production of valid results. ISO 17025 incorporates all ISO 9001 requirements relevant to the scope of testing services and further specifies the technical requirements for technical competence of a laboratory. It is applicable to all organizations performing tests, including laboratories where testing is part of product certification. ISO 17025 certifies that quality-oriented tests are performed correctly, establishing that the product (biological sample or derivative) is a quality product. All aspects of QC activities are examined by this standard. The qualification, education, and training of personnel are examined against job responsibilities. Every quality critical specification, including the qualifications of suppliers and collaborators, is checked. To be ISO17025 accredited, a biobank must not only be consistent, but also proficient in testing the quality of their products (biological samples or derivatives) [12].

In addition, the ISO 17034:2016 (General Requirements for the Competence of Reference Material Producers) concerns manufacturers of references materials or certified reference materials. All methods used by the manufacturer to certify their materials must be validated and proven accurate. It requires that any uncertainties, which include all of sources of error involved in characterizing the materials, be reported on the Certificate of Analysis. ISO 17034 provides the highest level of QA, stating that the manufacturer's materials are produced correctly and competently. Currently, the ATCC is the only biobank accredited with ISO 17034 for bacterial, fungal, and cell line cultures. The role of biobanks as reference material producers is discussed in the following chapter.

Existing guidelines for biobanks have been compiled into a single document according to the structure of ISO accreditation standards [13, 14] and incorporating color coding to allow the reader to distinguish between the original texts. This document contains previously published Best Practices that biobanks should follow if they wish to demonstrate that they operate a quality system and are able to provide biological samples that conform to specified requirements.

4 Biospecimen Quality Control

4.1 Sample Characterization

Homogeneity of collection procedures, shipping and storage conditions is critical to the quality of multicenter research studies. QC procedures are designed to ensure data and sample quality. Data QC includes control of demographic, pathology,

clinical, processing data accuracy, while biospecimen QC includes assays on sample authenticity, integrity and identity [15]. Biospecimen QC is required to ensure accurate sample characterization and categorisation and avoid introducing bias in downstream research due to intrinsic heterogeneity in samples. Accurate characterization of the samples supplied by a biobank concerns both the authentication and the integrity of the biomaterial.

Effective QC can be performed by biobanks in a number of ways. QC can be performed on every specimen received; this is strongly recommended and cost-effective in some cases, e.g. hemocytometry on all incoming blood samples. QC can be performed on every sample going into storage, e.g. quantification and purity of all DNA samples. QC can be performed on outgoing samples, before their distribution to researchers, e.g. RNA integrity measure, provided it is not destructive to the samples.

QC assays may be performed by the biobank, the end user or a sub-contracting laboratory. They should be done by the biobank according to GLP (Good Laboratory Practice), or where a biobank does not have the facility, by a subcontracted laboratory compliant to ISO 15189:2012 (Medical Laboratories—Particular Requirements for Quality and Competence), to ISO 17025:2005 or to CLIA (Clinical Laboratory Improvement Amendments). Retrospective QC may be applied to either a randomly selected percentage of the collected specimens or to samples considered to have undergone the most "inconsistent" processing. The first approach allows comparisons between different collection sites and the second allows targeted assessment of the "highest risk" samples.

4.2 Sample Authenticity and Integrity

Sample authenticity refers to providing a guarantee that a sample is indeed what it is refers to as, such as when a biobank provides a serum sample from a patient with primary melanoma, there must be proof of the primary melanoma (authenticity) and that the sample was not compromised by any pre-analytical bias (integrity). In this case, QC requires a histopathologic validation on fixed and/or frozen sections to validate the tissue sample. The evaluation must be performed by a trained pathologist to confirm the tissue type (tumor or normal) and the basic histopathological diagnosis and classification (International Classification of Diseases), based on standard hematoxylin-eosin staining. The test includes assessment of cellular composition, which is of critical importance in any downstream molecular analysis. Highly heterogeneous cellular composition makes molecular analysis irrelevant and the minimum percentage of tumor is often set at 70%. Standard histologic control also includes assessment of morphologic degradation. Histopathologic analysis allows identification and marking of the block areas which are the most suitable for tissue microarray cores. The exact nature of the integrity QC tests performed depends on the intended end use.

QC tests allowing assessment of processing, shipping and storage conditions may include microparticle counts in serum or plasma to assess centrifugation conditions and efficiency, platelet activation components to assess platelet activation during sample processing, serum sCD40L measurement to assess the time samples were exposed to ambient temperature [16], plasma protein S activity to assess cryostorage duration and conditions [17], matrix metalloproteinases in serum or plasma to assess storage conditions [18], hemoglobin measurement in serum or plasma to assess hemolysis which may have taken place during collection or prolonged pre-centrifugation delays of blood samples, and levels of cytokines such as G-CSF, CXCL10, MIF, serpin E1, CXCL12 in plasma samples, which decrease with increasing freeze-thaw cycles [16].

QC tests which allow more accurate sample characterization and ensure more efficient downstream analyses include (but are not limited to) C-reactive protein measurement in serum to assess inflammation degree and corresponding normalization of downstream proteomic analyses; creatinine and cystatin-C measurement in urine to normalize protein content in view of downstream proteomic analyses. Serum IgM detection in acutely infected patients allows assessment of the possible use of the serum samples in immunologic assays targeting specific IgM. Assessment of tissue integrity by immunohistochemistry may include vimentin, cytokeratin, surface kinases, hypoxia-related molecules and hormone receptors. Serum fingerprinting can be performed to assess the identity of different serum samples [19].

DNA QC assays include DNA quantification and purity analysis by spectrophotometry/fluorometry and gel electrophoresis. PCR assays can assess the DNA cross-linking degree and fitness-for-purpose in downstream whole genome amplification or comparative genomic hybridization arrays [20]. Possible inhibitors can be detected by the SPUD real-time PCR assay [21].

RNA QC assays include total RNA quantification by spectrophotometry/fluorometry and RNA integrity assessment by RNA Integrity Number (RIN) measure. Reverse transcriptase (RT)-PCR, by amplification of specific cDNA targets (eg. GAPDH) using combinations of primers designed to amplify fragments with progressively increasing sizes (100, 200, 300, and 400 basepairs) can be used to assess the maximum amplifiable size of RNA. miRNAs, which are increasingly used in cancer research can be measured with real-time RT-PCR for ubiquitously expressed miRNAs, such as the miR16.

Samples used as a reference in diagnostic commercialized kits must be tested for HIV, HBC and HCV. This can be performed by a central QC laboratory. The critical steps in each assay should be documented and controlled.

QC assays used to characterize biospecimens are different for viable and non-viable specimens. Viability and functionality (e.g. pluripotency, response to antigens, motility) are assessed through microscopy, flow cytometry or immunoenzymatic assays. For non-viable specimens, molecular integrity (e.g. protein phosphorylation status, epitope conformation, rRNA degradation, DNA cross linking degree) is generally assessed through immunoenzymatic, electrophoretic and molecular biology assays [20].

5 Tools for Assisting QA/QC Implementation

5.1 Self-Assessment Tool

In 2009, the ISBER developed a self-assessment tool (SAT) to assist individuals managing repositories in determining how closely their organization conforms to the ISBER Best Practices for Repositories [22]. The assessment is confidential and allows biorepositories and biobanks to strengthen their practices by identifying areas in need of improvement. The survey consists of 158 questions that are divided into sections corresponding to sections of the ISBER Best Practices. Participants receive personalized feedback that includes a risk-balanced assessment score measuring the level of risk to the specimens for a given practice, the frequency of implementation of each practice, and the ease with which deviations from the recommended practice can be detected. The score can be used to evaluate how closely their current practices conform to the recommendations. In addition, participants are notified of the most critical areas in which their responses deviate from the recommended best practices.

5.2 Method Validation

Method validation is an important aspect in all sample or derivative characterization assays, and is an essential requirement of the ISO 17025. Method validation provides confidence that detected analytical differences are due to true clinical differences and not to different organism strains, different human genetic backgrounds, or different methodologies.

Several recent studies have recognized the influence of preanalytical variables (e.g. warm/cold ischemia times, or delays in processing) on the integrity of biomolecules or gene expression [23, 24]. The potential impact of these influences is illustrated in the case of gene profiling of peripheral blood cells to identify biomarkers for improving diagnosis and clinical management, where variables that may alter gene expression would result in artefactual changes unrelated to the disease of interest. Identifying and controlling potential bias in molecular analyses which can result from biospecimen processing remains a fundamental challenge to biobank QA and biospecimen science.

Biobanking processing method validation requires knowledge of both the preanalytical variables that need to be controlled as well as factors that do not impact the quality of the biospecimen for a given type of research. Controlling preanalytical variables is a particularly challenging and complex issue, since the influence of a sample's quality on the molecular data obtained from its analysis depends on both the nature of the biomolecule analyzed (DNA, RNA, protein, metabolite), the type of analytical method (multiplex vs singleplex; qualitative vs quantitative), and the specificity, sensitivity, and robustness of the method with respect to specific preanalytical variations.

To address these issues, three main approaches are used in biospecimen science-driven biobanking. The first is to validate the biospecimen processing methods. Processing method validation includes validation of the reproducibility, the robustness and the fitness-for-purpose of the method [25]. The second is to optimize the quality of biospecimens and thus directly minimize and/or control the preanalytical bias. However, in most clinical settings the ability to control certain preanalytical variables influencing biomolecule integrity, such as surgery or warm ischemia time, is limited. To counter this, a third approach ensures appropriate tests are applied retrospectively to accurately assess the global biomolecular integrity of each biospecimen. This process is critical for high-throughput, quantitative downstream assays implemented in clinical molecular diagnostics.

Once the key points in a biospecimen processing method have been identified, specific tests or markers to assess the biospecimen quality are needed. These may be called "surrogate quality biomarkers" or "quality indicators". Currently, there are few appropriate QC tools that are predictive of downstream method feasibility (e.g. DNA cross-linking and CGH array applications) and reliability (e.g. feasibility of CGH array analysis does not guarantee its accuracy), or are diagnostic of upstream biospecimen processing steps (e.g. tissue fixation time). QC, in the form of diagnostic tests for upstream biospecimen processing steps is termed "biospecimen molecular diagnostics" or "preanalytical characterization". Ultimately, preanalytical characterization should allow researchers to assess the reliability of specific downstream analyses, done with the samples. A Technical Report, presenting the assays that can be used for qualification or quality stratification of clinical biospecimens has been published by the ISBER Biospecimen Science Working Group [26].

5.3 SPREC, a System for Documenting Pre-Analytic Conditions

The concept of "quality" with respect to biospecimens cannot be uniquely defined since processing conditions optimizing a specimen for use vary according to the downstream analyses. If samples are intended to be used for immunological, molecular biology, or proteomic analyses, critical *in vitro* preanalytical steps should be accurately recorded for biological fluids or solid tissues collected. For biological fluids, this information includes type of primary collection tube, pre-centrifugation time delay and temperature, centrifugation conditions, post-centrifugation time delay and temperature, and long-term storage duration and temperature. For solid tissues, it includes warm and cold ischemia times, type and duration of fixation, and long-term storage duration and conditions. If samples will be used in metabolomics applications, *in vivo* preanalytical data including the time of the day when the samples were collected, and food and medication intake should also be collected.

Sample management to ensure its quality and suitability for specific purposes requires meticulous documentation of the conditions of collection, processing and storage. Consistency of sample quality can be ensured by (1) rigorous documentation of preanalytical steps (prospective collections), and by (2) QC assays, diagnostic for a sample's preanalytics and for fitness-for-purpose (historical collections).

The ISBER has developed a system for identifying and documenting pre-analytical factors that can impact the integrity of biospecimens and their simple derivatives during collection, processing and storage. The SPREC (Standard PRE-analytical Code) is a specimen or pre-analytical "barcode" recording details about pre-analytical sample processing in a standardized format [27]. It is a 7-element code, where each element corresponds to a critical pre-analytical variable. It can be applied to both primary samples and derivatives. For fluid samples, the SPREC contains information on the sample type, type of primary container, initial and subsequent centrifugation conditions, conditions (delay and temperature) between collection and processing and between centrifugation and storage, and long-term storage conditions. For solid samples, SPREC reports on the nature of the sample and method of sampling, warm/cold ischemia times, fixation type and time, and long-term storage conditions. Tables 1 and 2 present the SPREC version 02 [28].

This simple code assists researchers and biobankers to identify the most important pre-analytical variables associated with a sample. It is easy to understand and does not require special knowledge, simply "good recording practices" and can be used via a free online tool. Implementation leads to an increased awareness among the medical, scientific and technical staff implicated in the process, of the importance of accurate and standardized sample collection and processing, thus reducing deviations from established processes and improving sample quality. For biobanks with formal QMS, SPREC annotation of samples and regular evaluation against project-specific or general quality targets permits quantitative measurement of quality objectives. This allows the biobank to implement corrections or improve its processes.

The selection of a sample for a specific research project takes into consideration biological, clinical and pre-analytical components. The scientific community needs to agree on data elements that should be documented in scientific publications, as proposed in the Biospecimen Reporting for Improved Study Quality (BRISQ) recommendations [29]. Samples qualified with SPREC and BRISQ [30] data items, have a high value for end users, since biological samples and their annotations (clinical as well as pre-analytical data) should not be dissociated. Combined use of samples from multiple biobanks can be achieved more efficiently, due to an unambiguous, very simple and easily shareable sample description. It can significantly reduce potential misunderstandings about the suitability of samples for end users' purposes and thus avoid inappropriate experiments.

Table 1 Preanalytical variables, version SPREC 2.0, applied to fluid samples

Type of sample	
Ascites fluid	ASC
Amniotic fluid	**AMN**
Bronchoalveolar lavage	**BAL**
Blood (whole)	**BLD**
Bone marrow aspirate	**BMA**
Breast milk	**BMK**
Buccal cells	**BUC**
Unficolled buffy coat, viable	**BUF**
Unficolled buffy coat, non-viable	BFF
Ficoll mononuclear cells, viable	**CEL**
Fresh cells from non-blood specimen type	**CEN**
Cells from non blood specimen type (e.g. ascites, amniotic), viable	**CLN**
Cord blood	**CRD**
Cerebrospinal fluid	**CSF**
Dried whole blood (e.g. Guthrie cards)	**DWB**
Nasal washing	**NAS**
Ficoll mononuclear cells, non viable	**PEL**
Cells from non blood specimen type (e.g. ascites, amniotic), non-viable	**PEN**
Pleural fluid	**PFL**
Plasma, single spun	**PL1**
Plasma, double spun	**PL2**
Red blood cells	RBC
Saliva	**SAL**
Semen	**SEM**
Serum	**SER**

Sputum	**SPT**
Stool	**STL**
Synovial fluid	SYN
Tears	**TER**
24 h urine	U24
Urine, random (“spot”)	**URN**
Urine, first morning	URM
Urine, timed	URT
Other	ZZZ
Type of primary container	
Acid citrate dextrose	**ACD**
Additives	ADD
Serum tube without clot activator	CAT
Citrate phosphate dextrose	**CPD**
Cell Preparation Tube®	CPT
EDTA and gel	EDG
Lithium heparin	**HEP**
Hirudin	HIR
Lithium heparin and gel	**LHG**
Oragene collection container *or equivalent*	**ORG**
PAXgene® blood RNA+	**PAX**
Potassium EDTA	**PED**
Polyethylene tube sterile	PET
S8820 protease inhibitor tablets *or equivalent*	**PI1**
Protease inhibitors	PIX
Polypropylene tube sterile	PPS

(continued)

Table 1 (continued)

PAXgene® blood DNA		PXD
PAXgene® bone marrow RNA		PXR
Sodium citrate		**SCI**
Sodium EDTA		**SED**
Sodium heparin		SHP
Sodium fluoride/potassium oxalate		**SPO**
Serum separator tube with clot activator		**SST**
Tempus® tube		**TEM**
Trace elements tube		TRC
Unknown		XXX
Other		ZZZ
Pre-centrifugation (delay between collection and processing)		
RT[a]	<2 h	A
2–10 °C	<2 h	B
RT	2–4 h	C
2–10 °C	2–4 h	D
RT	4–8 h	E
2–10 °C	4–8 h	F
RT	8–12 h	G
2–10 °C	8–12 h	H
RT	12–24 h	I
2–10 °C	12–24 h	J
RT	24–48 h	K
2–10 °C	24–48 h	L
RT	>48 h	M
2–10 °C	>48 h	N

35–38 °C	<2 h	O
Unknown		X
Other		Z
Centrifugation		
RT 10–15 min	<3000 g no braking	A
RT 10–15 min	<3000 g with braking	B
2–10 °C 10–15 min	<3000 g no braking	C
2–10 °C 10–15 min	<3000 g with braking	D
RT 10–15 min	3000–6000 g with braking	E
2–10 °C 10–15 min	3000–6000 g with braking	F
RT 10–15 min	6000–10,000 g with braking	G
2–10 °C 10–15 min	6000–10,000 g with braking	H
RT 10–15 min	>10,000 g with braking	I
2–10 °C 10–15 min	>10,000 g with braking	J
RT 30 min	<1000 g no braking	M
No centrifugation		N
Unknown		X
Other		Z
Second centrifugation		
RT 10–15 min	<3000 g no braking	A
RT 10–15 min	<3000 g with braking	B
2–10 °C 10–15 min	<3000 g no braking	C
2–10 °C 10–15 min	<3000 g with braking	D
RT 10–15 min	3000–6000 g with braking	E
2–10 °C 10–15 min	3000–6000 g with braking	F
RT 10–15 min	6000–10,000 g with braking	G

(continued)

Table 1 (continued)

2–10 °C 10–15 min	6000–10,000 g with braking	H
RT 10–15 min	>10,000 g with braking	I
2–10 °C 10–15 min	>10,000 g with braking	J
No centrifugation		N
Unknown		X
Other		Z
Post-centrifugation delay		
<1 h 2–10 °C		A
<1 h RT		B
1–2 h 2–10 °C		C
1–2 h RT		D
2–8 h 2–10 °C		E
2–8 h RT		F
8–24 h 2–10 °C		G
8–24 h RT		H
>24 h 2–10 °C		I
>24 h RT		J
Not applicable		N
Unknown		X
Other		Z
Long-term storage		
PP tube 0.5–2-mL[b]	(−85) to (−60) °C	A
PP tube 0.5–2-mL	(−35) to (−18) °C	B
PP tube 0.5–2-mL	<−135 ° C	V
Cryotube 1–2-mL	LN[c]	C
Cryotube 1–2-mL	(−85) to (−60) °C	D

Cryotube 1–2-mL	Programmable freezing to <−135 °C	E
Plastic cryo straw	LN[c]	F
Straw	(−85) to (−60) °C	G
Straw	(−35) to (−18) °C	H
Straw	Programmable freezing to <−135 °C	I
PP tube ≥5 mL	(−85) to (−60) °C	J
PP tube ≥5 mL	(−35) to (−18) °C	K
Microplate	(−85) to (−60) °C	L
Microplate	(−35) to (−18) °C	M
Cryotube 1–2-mL	LN[c] after temporary (−85) to (−60) °C	N
Plastic cryo straw	LN[c] after temporary (−85) to (−60) °C	O
Paraffin block	RT[a] or 2–10 °C	P
Bag	LN[c]	Q
Dry technology medium	RT	R
PP tube 40–500-L	(−85) to (−60) °C	S
PP tube 40–500-L	(−35) to (−18) °C	T
PP tube 40–500-L	<−135 ° C	W
Original primary container	(−35) to (−18) °C or (−85) to (−60) °C	Y
Unknown		X
Other		Z

Codes in bold come from the Laboratory Data Management System (LDMS)
Volumes refer to container size
[a]RT, room temperature: 18–28 °C
[b]PP, polypropylene
[c]LN, liquid nitrogen, referring to either vapor- or liquid-phase (this information being documented in the biobank's SOPs)

Table 2 Preanalytical variables, version SPREC 2.0, applied to solid samples

Type of sample	
Fresh cells from non blood specimen type (e.g. biopsy)	**CEN**
Cells from non blood specimen type (e.g. dissociated tissue), viable	**CLN**
Cells from fine needle aspirate	FNA
Hair	**HAR**
Cells from laser capture microdissected tissue	LCM
Cells from non blood specimen type (e.g. dissociated tissue), non viable	**PEN**
Placenta	**PLC**
Solid tissue	**TIS**
Disrupted tissue, non-viable	TCM
Other	ZZZ
Type of collection	
Autopsy <6 h post-mortem	A06
Autopsy 6–12 h post-mortem	A12
Autopsy 12–24 h post-mortem	A24
Autopsy 24–48 h post-mortem	A48
Autopsy 48–72 h post-mortem	A72
Biopsy in culture media	BCM
Biopsy	**BPS**
Biopsy in normal saline or phosphate buffered saline	BSL
Biopsy in tissue low temperature transport media	BTM
Fine needle aspirate	FNA
Punction	PUN
Surgical excision in culture media	SCM
Surgical excision	SRG
Surgical excision in normal saline or phosphate buffered saline	SSL

Surgical excision in tissue low temperature transport media	STM
Surgical excision in vacuum container	VAC
Swab	**SWB**
Other	ZZZ
Warm ischemia time	
< 2 min	A
2–10 min	B
10–20 min	C
20–30 min	D
30–60 min	E
>60 min	F
Unknown	X
Not applicable (e.g. biopsy)	N
Other	Z
Cold ischemia time	
< 2 min	A
2–10 min	B
10–20 min	C
20–30 min	D
30–60 min	E
>60 min	F
Unknown	X
Not applicable (e.g. autopsy)	N
Other	Z
Fixation/stabilization type	
Non-aldehyde with acetic acid	ACA

(continued)

Table 2 (continued)

Aldehyde-based		ALD
Allprotect ® tissue reagent		ALL
Alcohol-based		ETH
Non-buffered formalin		FOR
Heat stabilization		HST
Snap freezing		**SNP**
Non-aldehyde based without acetic acid		NAA
Neutral buffered formalin		NBF
Optimum cutting temperature medium		**OCT**
PAXgene® tissue		PXT
RNA Later®		**RNL**
Unknown		XXX
Other		ZZZ
Fixation time		
<15 min		A
15 min to 1 h		B
1–4 h		C
4–8 h		D
8–24 h		E
24–48 h		F
48–72 h		G
Not applicable		N
Unknown		X
Other		Z
Long-term storage		
PP tube 0.5–2-mL[b]	(−85) to (−60) °C	A
PP tube 0.5–2-mL	(−35) to (−18) °C	B

PP tube 0.5–2-mL	<−135 ° C	V
Cryotube 1–2-mL	Liquid nitrogen[c]	C
Cryotube 1–2-mL	(−85) to (−60) °C	D
Cryotube 1–2-mL	Programmable freezing to <−135 °C	E
Plastic cryostraw	Liquid nitrogen	F
Straw	(−85) to (−60) °C	G
Straw	(−35) to (−18) °C	H
Straw	Programmable freezing to <−135 °C	I
PP tube ≥5 mL	(−85) to (−60) °C	J
PP tube ≥5 mL	(−35) to (−18) °C	K
Microplate	(−85) to (−60) °C	L
Microplate	(−35) to (−18) °C	M
Cryotube 1–2-mL	LN[c] after temporary (−85) to (−60) °C	N
Straw	LN[c] after temporary (−85) to (−60) °C	O
Paraffin block	RT[a] or 2–10 °C	P
Bag	LN[c]	Q
Dry technology medium	RT	R
PP tube 40–500 L	(−85) to (−60) °C	S
PP tube 40–500 L	(−35) to (−18) °C	T
PP tube 40–500-L	<−135 ° C	W
Original primary container	(−35) to (−18) °C or (−85) to (−60) °C	Y
Unknown		X
Other		Z

Codes in bold come from the Laboratory Data Management System (LDMS)
Volumes refer to container size
[a]RT, room temperature: 18–28 °C
[b]PP, polypropylene
[c]Liquid nitrogen refers to either vapor or liquid phase (this information being documented in the biobank's SOPs)

6 Addressing QA/QC Gaps

While both international and national certification norms exist, none of the international norms are specific to biobanks, while none of the national biobanking norms cover all biobank technical specificities, revealing some clear gaps in the current system. Likewise, there is a need to standardize the assays used to assess molecular integrity of biospecimens procured in a clinical setting.

This gap can be defined as an absence of technical specifications including requirements and methodologies for validating biospecimen processing. Current standards include requirements for validation of testing methods (where the output is an analytical measurement) but not for validation of processing methods (where the output is a sample), with integration of the different steps during bioprocessing (tube and rack formats, LIMS integration, traceability of the whole bioprocessing chain, time stamps etc). The gap is broadening as novel specimen collection and processing methods are commercialized (e.g. room temperature technologies, whole genome amplification) without adequate validation.

In 2013, an ISO Technical Committee, ISO/TC 276 dedicated to biotechnology-related issues, which are either not addressed or poorly addressed was established. For biobanking, this principally concerns validation of biospecimen processing methods. Biobanks typically process materials using previously published protocols or those communicated by colleagues. However, in both cases formal validation in terms of a demonstration of the reproducibility, robustness, stability and fitness-for-purpose of the biospecimen processing method for downstream applications is lacking.

If the issue is not addressed, biobanks will continue to produce biospecimens applying non-validated methods, and thus producing specimens which may not be fit-for-purpose or of comparable quality. Consequences are heavy in terms of loss of time and money by the industrial and academic biotechnology application scientists, wasted specimen donations, and also unreliability of clinically relevant biomarker identification—which is obviously critical to diagnostics. As long as this remains the *status quo*, quality of the output will be compromised, hampering international collaborations between biotechnology application scientists.

6.1 Technical Specification Documents

One way to address this gap is to introduce ISO technical standards, in the form of ISO Technical Reports (TR) and ISO Technical Specifications (TS).

Three groups of technical standards are needed. The first group is for informative Technical Reports on processing and qualification (e.g., “Processing and qualification of tumor tissue specimens”, “Processing and qualification of fecal specimens”). These should include information on processing methods (further elaborated in a second group of Technical Specifications), definition of material properties,

performance metrics, and validation protocols with well-defined analytical endpoints (further elaborated in a third group of Technical Specifications) and specific acceptance criteria.

The second group is for Technical Specifications on specific bioprocessing methods (e.g., "Protein extraction from FFPE tissue", "Human tissue culture"). These should include evidence-based recommendations and methodology for the validation of bioprocessing in terms of performance (or "fitness-for-purpose"), reproducibility (or "consistency"), robustness to pre-analytical variations, biosafety, and stability.

The third group is for Technical Specifications on specific biospecimen QC methods (e.g., "Methods to determine the relative accuracy of cell counting methods", "Methods to determine the concentration of total nucleic acids"). Such a system of ISO technical standards would offer modularity and flexibility, and could be used either in combination with ISO9001 (or equivalent) certification or in combination with ISO 17025 (or equivalent) and ISO 17034 accreditation (Fig. 1).

6.2 External Quality Assurance/Proficiency Testing

External quality assurance (EQA) refers to an objective method that allows for comparison of a laboratory's testing to an external source—either a peer group of laboratories or a reference laboratory. In the context of biobanks, it can assess (1) performance of specimen processing or (2) accuracy of specimen testing.

Performance (1) can be assessed indirectly by evaluating performance in processing, producing, and storing of biospecimens relative to metrics collected by a central laboratory. The central laboratory produces an average (e.g., DNA yield or ratio) obtained from all participating biobanks, and assesses the performance of each participant relative to others. This evaluation is notably performed with respect to challenging materials, such as DNA or RNA extracted from FFPE tissues.

A second EQA option (2) which is taking on an increasingly prominent role is proficiency testing (PT), such as the ISBER-endorsed IBBL PT program [31]. This program allows a biobank to evaluate the accuracy of their sample testing methods and compare their results with other laboratories. PT can be used to identify interlaboratory differences, testing problems that may be related to individual staff performance or calibration of instrumentation used in biospecimen QC and provide guidance for remedial actions. It can also be used to determine the performance characteristics of new biospecimen QC methods and comparability with current methods. PT programs provide an additional layer of confidence to biospecimen end users, offering a means of accreditation, while also promoting collaboration between academic biobanks and the diagnostic and pharmaceutical industries. These programs are expected to improve biobank QMS and promote the quality and the economic health of the biobank industry by diminishing the "asymmetric information gap" between biospecimen providers and biospecimen end users.

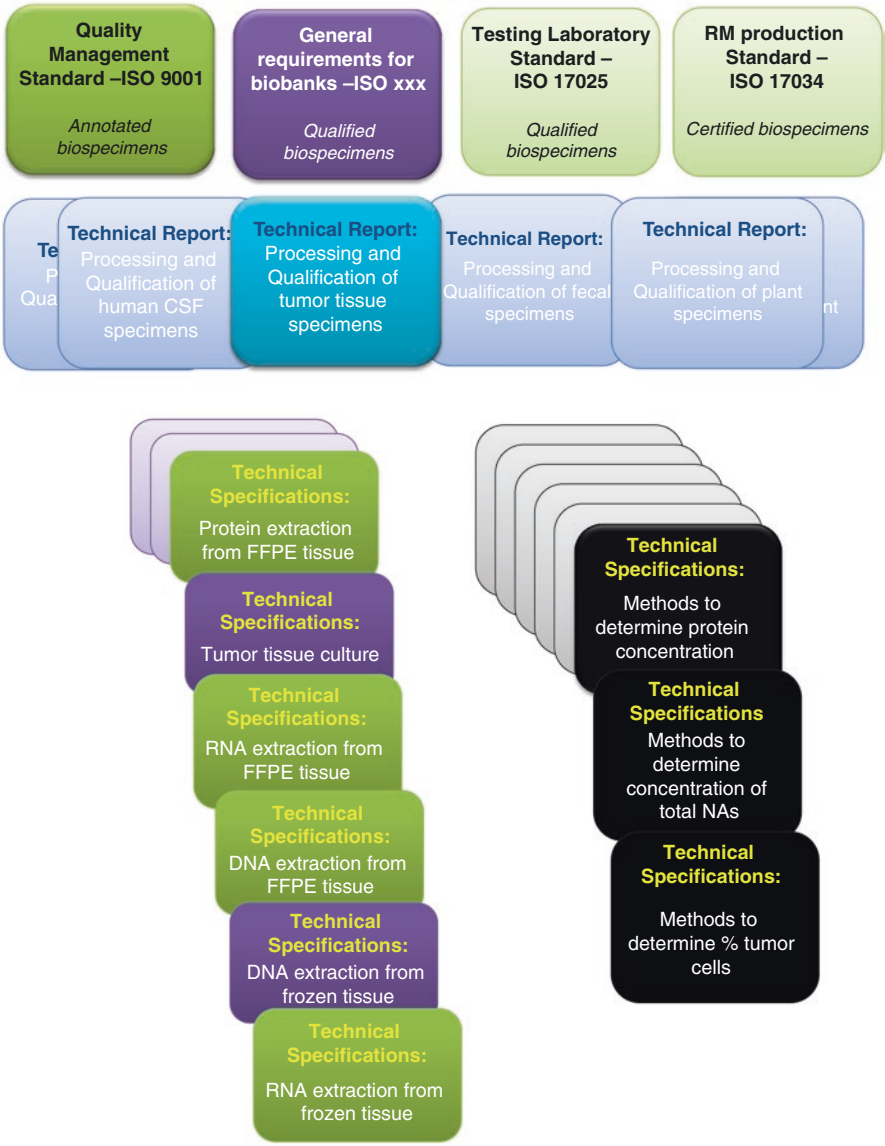

Fig. 1 Application of existing international standards (in green) to biobanks, in combination with—not yet existing—specific technical standards (in colours other than green)

The potential of the ISBER-endorsed PT Program lies in the development and implementation of schemes providing objective characterization of biospecimens that are independent of the specific processing method that has been used for their preparation and storage. Advancing the collaboration between academic biobanks and the diagnostic and pharmaceutical industries is an important step for the biobank

community. Accreditation of laboratories for performing these QC assays is a desirable future outcome of PT programs and could represent a major service of technical assistance to biobanks and/or sample end users [32].

6.3 Biobanks as Reference Material Producers

Some biobanks may fall under the definition of reference material producers as 'technically competent bodies that are fully responsible for assigning the certified or other property values of the reference materials they produce and supply which have been produced in accordance with ISO 17034' [33]. ISO 17034, in combination with ISO 17025, meets the need of these biobanks for a technical standard as envisaged by the International Laboratory Accreditation Cooperation (ILAC) General Assembly in October 2004 [34]. This General Assembly had resolved that accreditation of technically competent bodies producing reference materials with assigned values must be conducted according to harmonized criteria based on ISO Guide 34 and ISO/IEC 17025. When biobanks carry out some specific testing, such as safety testing for blood-borne viruses, they are not attempting to fully characterize the samples. As such, they are not producing well-characterized materials in the same sense as a reference material producer. Some biobanks do not carry out any testing on the samples collected at all, because of the limited nature of the material. Use of ISO 17025 and ISO 17034 is not appropriate for these biobanks. See the following chapter for a review of biobanks as RM producers.

7 Towards a Global Biobank QA System

Biological samples and associated data from biobanks will be accepted by academia and industry as fit-for-purpose if biobanks are required to be certified and/or accredited to international standards. [35].

Figure 1 shows the optimal combination of existing and necessary new normative tools of quality assurance for biobanks. The current international normative framework (ISO) includes QMS and testing laboratory standards, which can be applied to biobanks. Furthermore, the European Committee CEN/TC140 "In vitro diagnostic medical devices" has recently developed eight Technical Specification standard documents addressing specific processing methods ("specifications for pre-examination processes"). However, the current system lacks technical standards including the general requirements for biobanks, but also technical standards applicable to specific biobank fields (as outlined in 1.6.1). Such specific technical standards are yet to be developed by ISO.

For the moment, professional biobanks can be certified to existing general QMS standards, and produce consistently "annotated specimens". Some biobanks can either be accredited to existing laboratory standards or collaborate with accredited

laboratories, and produce “qualified specimens”. Finally, some biobanks can be accredited as reference material producers meeting international standards, which also exist, and produce “certified specimens” (as further discussed in the next chapter).

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Economics of Biobanking

Jim Vaught and Peter H. Watson

Abstract The economics of biobanking is an area that has traditionally been overlooked as biospecimen resources have been developed and expanded over the past 20 years. The explosive growth of interest in biobanking, and in the value of biospecimens and data that they collect and disseminate, has led to the necessity to adopt professional standards and practices, including business plans. There are a number of factors to consider in developing a biobank business plan, and some of these issues are unique to biospecimen resources. The costs of developing and maintaining a biobank are often difficult to assess given the traditional methods of funding including centralized institutional funding. Among the approaches to developing a business plan is the assessment of such costs and implementation of a cost-recovery plan. However such plans are difficult to implement or not allowed by institutional rules, and smaller biobanks may not be in a position to devote resources to developing and implementing a business plan. A broader approach that plans for the long-term sustainability of a biobank or biobanking network within a framework that considers the size and mission of the resource is now evolving.

Keywords Biobanking • Biobanking economics • Sustainability • Biospecimen • Economic impact

1 Introduction

In an editorial in *Biopreservation and Biobanking* entitled "Economics: The Neglected "Omics" of Biobanking" [1], the topic of biobanking economics was introduced as follows:

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> "In recent years, as biobanking has progressed to encompass all other "–omics" analyses, including genomics, proteomics, metabolomics, transcriptomics and the like, this sort of economic analysis has been lacking. Although several major economic models have been developed to sustain biobanks, funding is often supported by centralized budgets within institutions. This arrangement can lead to poor long-term management as the various stakeholders are unaware of the true cost of operating the facility. Often, those costs are not itemized in a way that individual users can understand. And not being accountable for the costs of their individual collections can lead to wasteful practices, including costly long-term storage of unused specimens."

In this chapter we discuss the general economic and funding issues faced by biobanks and the approaches necessary for long-term sustainability. It should be noted that within the discipline the term biobank applies to a broad spectrum of entities [2] which range from large complex biobanks to small one-room, one-freezer operations. As discussed by Watson et al. [3] the need for and factors involved in sustainability differ across this spectrum. The primary focus of this chapter is therefore on biobanks that have been organized as central institutional facilities serving multiple stakeholders [3].

2 Fundamental Issues in Biobanking Economics

Funding for biobanks is often provided from central institutional budgets, or from multiple departmental budgets as either direct costs or from indirect or overhead funds. There is often no detailed business plan to allow for proper budgeting and cost control. Investigators who are responsible for collections may be unaware of the cost of collecting, processing and storing samples.

2.1 Costs of Establishing and Maintaining Biobanks

The infrastructure costs of establishing a medium to large sized biobank is generally in the millions of U.S. dollars [4]. The initial investment, using the example of a biobank of frozen tissue or liquid biospecimens, involves purchasing freezers, alarm systems and other security equipment, back-up generators, air-handling systems, and assorted equipment and supplies, as well as a data management system, to support biospeicmen collection, processing and storage as appropriate for the facilities [5]. In addition, the initial development of a biobank requires strict attention to validating the performance of equipment and the costs of establishing and maintaining a quality management system [5].

Depending on the biobank's purpose this initial large investment may be followed by a period of months or years of steady-state spending. However, there are ongoing costs that need to be itemized and budgeted for, as shown in Fig. 1. The items outlined in this example are high-level and do not account for all costs that may be encountered by all types of biobanks. Some of these costs, such as shipping rates and pathology review charges may be applied as in-kind or normal institutional costs that are well-established. However, it is often more difficult to itemize

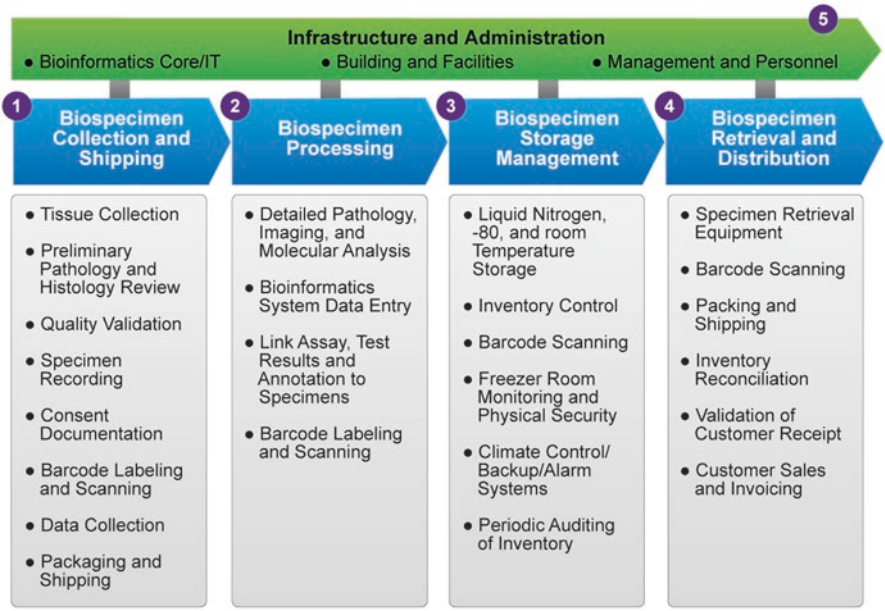

Fig. 1 The four major components of biobank operational costs, and a partial list of costs within the four components (adapted from reference [5], used with permission)

the cost of obtaining patient consent, data collection, quality validation and other costs that require maintaining records of personnel time performing specific tasks. In order to properly budget and track such biobank costs, it is necessary to develop at least a basic cost structure that can account for such costs.

2.2 Recovering Costs: Is Full Cost Recovery Possible?

Cost recovery is one method that biobanks could use to achieve long-term sustainability. However, a biobank's ability to recover costs is often limited by several factors. First, by definition the end user or customer of the research biobank is a researcher who also by definition pursues a dynamic, evolving, and demanding activity (i.e. research), generating new ideas and examining these with new technologies. Predicting the future needs of research is an important element in planning for which charges can be levied. Decisions around specialized case collections and the extent of up-front costs that can be incurred by the biobank at the time of collection, and initial processing and format for storage are difficult but can be critical when the research value may only emerge many years later, when for example patient outcome data is available. This can be challenging for biobanks and significantly influence the proportion of costs eventually recoverable by user fees. Commercial biobanks, such as those supported by pharmaceutical companies, or

commercial tissue brokers, may be required to recover a significant portion of their costs, or even make a profit. This is not the common situation for most academic, government and clinical biobanks which are not in a position to achieve significant cost recovery. Often the institutional governance, other sources of funding, stakeholder conditions, or prior commitments made to donors, create limits to the scale of user fees to modest recovery of for example the costs of retrieving, packaging and shipping samples to clients and collaborators. Other important factors for many academic biobanks are the extent to which the typical grant funding mechanisms will accommodate inclusion of realistic costs to access biobanks and the value placed on higher quality biospecimens by academic investigators. While some national funding agencies such as the National Health and Medical Research Council in Australia [6] have published 'pricing guides' to encourage realistic budgeting in grant submissions, this is not universal. More importantly, there is little encouragement for investigators within the current funding environment to seek out biobanks with higher user fees and more costly biospecimens when it is still possible to publish in many high quality journals with limited peer review or editorial requirements for 'certification' around the known quality of biospecimens or accompanying data.

Another consideration is that the many types of biobanks support a broad spectrum of health research. For example, the spectrum in the biomarker research field can be considered in terms of basic discovery, translation and clinical delineation, clinical confirmation and validation, clinical implementation and evaluation. The relative importance of sustainability and value placed on costly implementation of quality management systems also changes across this spectrum. For example, discovery phase research may place little value on long term outcomes data or consistency of biobanking processes across many biospecimens when the primary focus is often on cellular location and context within tissues as determined by several assays examining gene structure to expression. Instead the value is placed on aspects such as individual specimen collection variables, pathological diagnosis and annotation of tissue composition. Most of these costs can be readily estimated by the biobank. As research progresses across this spectrum the need for known and standardized quality across large cohorts of biospecimens collected over sufficiently long periods to enable annotation with outcomes data and interrogation by standardized research assays increases in importance. Most of these costs are more difficult for the biobank to estimate and implement with the knowledge that recovery will be possible in the future. This would suggest that the issue of sustainability looms larger for biobanks supporting research at the clinical end than for those at the basic end of the spectrum.

However, if significant cost recovery is a goal for a biobank and is allowable according to institutional rules and other regulations, then the following should be considered (adapted from [5]):

- Building scale: depending on the type of biobank (commercial, academic, government, large, small), the specimen collections should be of sufficient size to

allow for cost recovery that will be sufficient for an adequate return on investment.
- Case mix: Build a collection that will attract users based on design factors such as biospecimen types collected, format and processing.
- Inventory turnover: Similarly, build a collection that will result in adequate use of samples. Otherwise as inventory builds with inadequate turnover, operational costs will be too high for long-term sustainability.
- Market price parity: Cost recovery must be realistic in order to be effective. Consider tiered pricing to allow for differences in ability to pay for samples, i.e. from commercial versus academic users. The U.S. NCI Cooperative Human Tissue Network is an example of a virtual network with an effective partial cost recovery approach [7].
- What costs to recover: these can range from recovering only the basic costs of retrieving and shipping samples to more elaborate approaches to recover a more significant proportion of sample collection, processing and long-term storage costs. But cost recovery, again, must be realistic according to the mission, size and structure of the biobank.
- Other potential sources of revenue: depending on the size and mission of the biobank, consideration can be given to charging for special services such as nucleic acid extraction, tissue microarray construction, data collection and processing, and other special processing services.

There are other important questions related to the above discussion that still need to be answered and will require further study:

- What is the "value" of specimens and data? As noted elsewhere in this chapter, specimens and data have both extrinsic (quantifiable) and intrinsic (historic) value. Both have to be considered in any economic assessment of biobanks and their effectiveness and sustainability.
- Costs of implementing best practices? Efforts need to be made to quantify these, and then to demonstrate the quantitative benefits of implementing best practices.
- Importance of quality management and evidence-based standard operating procedures to the ability to generate reproducible research outcomes.
- Economic benefits: can they be quantified?
- Efficiencies of scale. Are larger centralized biobanks and networks more cost-effective?
- Impact of more efficient informatics systems and declining data storage costs.

Table 1 shows several theoretical economic benefits from adoption of such practices (from reference [8]).

Table 1 Estimated economic benefits from adopting biobanking business practices discussed in this chapter (From Reference [8], reprinted with permission)

Economic benefits impact category	Annual value	10-Year value (discounted)
Reductions in the cost of clinical trials	$116.8	$454.6
Patient diagnosis and therapeutic care	$48.5	$169.5
Efficiencies from leveraging infrastructure	$14.8	$51.5
Avoidance of repeat experimentation	$4.2	$14.6
Benefits due to implementation of best practices	$2.4	$4.1
Industry job creation impact on economy	$0.1	$5.9
Improved modeling of clinical data	$0.5	$1.5
Total estimated economic benefits	*$187.3*	*$701.7*

Dollar estimates (in millions) for a number of economic benefits that a national biobank entity could directly contribute to the cancer research community

3 Business Planning in Biobank Best Practices

Business planning and other economic issues are now being addressed in biobanking best practices. The U.S. NCI Best Practices for Biospecimen Resources [9] address these issues in a Business Planning section, with the following recommendations:

- Business planning should provide justification for financial and institutional commitment and quantification of startup and sustainability costs.
- Business planning should be integrated into all aspects of operations, biospecimen resource management, and evaluation.
- Biospecimen resources should aim to establish a documented annual business plan developed with department staff input and aligned with the vision and mission of the resource. Business plan items should be specific, measurable, actionable, relevant, and time bound.
- The resource business plan should also include a formal continuity plan that addresses all possible operational disruptions, including disaster planning.
- If the resource functions as a service center, the business plan should address issues related to service and revenue generation.

The above proposed best practices assume that the biobank is part of an institution that has resources to produce and maintain such a business plan. In the case of small biobanks, less complicated approaches would be more appropriate, such as maintaining a basic accounting system to track costs and expenses or alignment with a larger institutional biobank.

Also see the 2012 edition of the ISBER *2012 Best Practices for Repositories Collection, Storage, Retrieval, and Distribution of Biological Materials for Research* [10], where Section H provides recommendations for: identifying and defining costs; cost analysis; and cost recovery.

4 Economics of Biobanking Networks

In their 2010 review of international biobanking networks, Vaught et al. [11] outlined the characteristics of 16 biobanking networks from diverse areas around the world. The information in the paper was gathered from public web sites. The biobank networks profiled in the *Biopreservation and Biobanking* review, although they operate under a variety of models, share many of the following characteristics, as detailed in their web sites:

- Governance models with clearly stated technical standards, ethical guidelines, access policies and procedures, scientific rationale, and long-term custodianship plans, i.e. assuring that the program is sustainable from a technical and economic perspective.
- A strong quality assurance/quality control program, with clearly defined standard operating procedures, and regular audits to assure compliance with established policies and procedures.
- A comprehensive business model that, unless the network and its members are entirely supported by public funds, includes a sustainable cost-recovery plan, or other means to assure consistent long-term financial support.
- In general, adherence to a set of best practices governing both technical and ethical/legal issues, such as those published by the International Society for Biological and Environmental Repositories [10] and NCI [9].

A good example of a biobanking network that has developed an effective business plan is the Canadian Tissue Repository Network [3, 12]. CTRNet is funded by the Institute of Cancer Research, Canadian Institutes of Health Research. This central funding plan is limited to support for network activities such as creating a biobank certification program and standard operating procedures and policies. CTRNet, in partnership with the University of British Columbia Office of Biobank Education and Research, has created the Biobank Resource Centre (BRC). As noted by Watson et al. [3] the BRC was established to "provide services and tools that support researchers in establishing and operating biobanks, to educate and promote certification of biobanks in order to enhance quality through adoption of best practice standards, and to publish biobank market research data." CTRNet and the BRC have been instrumental in establishing and publishing detailed information concerning biobanking costs, patterns of biospecimen use in research, approaches to improve customer focus, and cost recovery strategies [13]. Among the BRC's online biobanking tools is the Biobank User Fee Calculator (www.biobanking.org) which can be used to establish user fees to facilitate cost recovery and more general biobank business planning.

5 Historical Value of Biospecimen Collections

Biospecimens have an "extrinsic" value that can be quantified according to the factors discussed in previous sections of this chapter, that is, the cost of all of the processes involved in sample management can be documented. In addition, the operating costs for managing the biobank and the long-term "total life cycle cost of ownership" can be determined and used to develop and adhere to a business plan [5].

However biospecimens also have an "intrinsic" value that cannot be quantified in monetary terms, but which gives biobank collections significant long-term value. One such intrinsic factor is the long-term value of clinical or epidemiologic data collected and associated with biospecimens. Other examples originate from collections that are maintained for their potential historical value. In 2009 the U.S. Interagency Working Group on Scientific Collections [14] produced a report entitled "Scientific Collections: Mission-Critical Infrastructure for Federal Scientific Agencies." The report provides examples of the many diverse collections supported by U.S. federal agencies, for a variety of purposes. In terms of biological specimen collections, one example shows the tremendous historical value of samples that have been preserved from the 1918 Spanish influenza pandemic:

> "Researchers compared preserved samples of influenza virus taken from Smithsonian bird specimens with human tissue samples from the notorious 1918 Spanish flu pandemic, to determine that the disease was not a type of avian influenza, as had been previously thought, but rather was related to strains that commonly affected pigs and humans. This discovery of the pandemic's true vectors helped to guide the development of containment policy. Further study of the virus's evolutionary history has helped improve vaccine development."

This example not only shows the intrinsic value of maintaining such a collection, but also has a quantifiable economic impact, in that funds could be used more efficiently to develop vaccines using data gathered from the historic collection of samples.

Other examples of the intrinsic value of older biospecimen collections come from the U.S. Centers for Disease Control and Prevention [15]:

- Legionnaire's Disease: serum from more than 30 unresolved pneumonia-like outbreaks stored in serum bank were linked to the "new" disease; identified a new organism and detected antibodies in the archived samples.
- Hantavirus: used residual serum and blood from a CDC nutrition study conducted in the same Navajo reservation area 2 years earlier; showed Hantavirus was not a new organism and was present in approximately 6% in the population before environmental conditions made the outbreak possible.
- U.S. National Health and Nutrition Survey (NHANES): excess and reserve specimens given to investigators after the original surveys were completed allowed greater research power and identification of new biomarkers.
- HIV Collections: traced emergence of new strains over time.
- Hepatitis Strains: used older NHANES collections to track the emergence of these new strains over time in the U.S. population.

6 Biobankonomics

In 2011 the Biorepositories and Biospecimen Research group at the U.S. National Cancer Institute published a Journal of the NCI Monograph which included two "biobankonomics" papers [5, 8] with recommendations for developing a sustainable business model for a biobank. In addition to the cost analysis, the following items were recommended for consideration: Managing variations in the availability of funding; assessing the "market need" for specimens and data collected by the biobank; the long-term "total cost of ownership"; cost recovery and analysis of return on investment; effect of inventory turnover rates; and the development of public-private partnerships to achieve long-term sustainability. In the second of the two papers, the potential economic benefits of developing standardized, centralized biobanks were analyzed. These include quantifiable actions that have economic impact such as implementing strict standards to avoid repeat collection and analyses due to poor specimen quality. Other long-term economic impacts are less quantifiable without further study, but may include: Benefits due to strict adherence to best practices; lower costs for clinical trials and patient care due to production of better quality specimens and data; and efficiencies of scale if biospecimen resources choose to form a network or a centralized biobank that adheres to a set of standard practices.

7 Public-Private Partnerships for Long-Term Sustainability

The Moffitt Cancer Center-Merck Pharmaceuticals Partnership offers an example of how a partnership between public and private stakeholders may contribute to the business planning of biobanking initiatives. In 2005, the Moffitt Cancer Center in Florida partnered with patients, community clinicians, industry, academia, and 17 hospitals in the United States to begin a personalized cancer care initiative called Total Cancer Care [16]. The objective was to collect tumor specimens and clinical data throughout a patient's lifetime, with the goal of finding "the right treatment, for the right patient, at the right time." The program involved collecting clinical data and tumor specimens for research purposes, with a formal protocol and patient consent process, and a robust "warehouse" for clinical and molecular profiling data. An agreement was negotiated where Merck contributed funding and developed sample and data sharing policies and procedures in partnership with the Moffitt Cancer Center. As of 2011 more than 76,000 cancer patients from Moffitt and consortium medical centers were enrolled in the protocol. The Total Cancer Care initiative has developed many of the capabilities and resources that are building the foundation of personalized medicine.

In a follow-up analysis of the Total Cancer Care program, Craig et al. [17] proposed that the Moffitt-Merck partnership's integrated system of standardized data and specimen collection, through a public-private partnership, allows for efficiencies of scale and faster accrual of patients and tissue samples. They proposed that

centralized biorepositories and data warehouses allow for better assessment of resource allocation and investment and that translational research is facilitated. Through an analysis of the Total Cancer Care program's progress, they found that clinical trial size and duration can be reduced through standardization and faster accruals; resulting in scientific, economic and ethical advantages. This "value of information" approach could also lead to faster, more economical, development of cancer therapies.

8 Planning for Long-Term Sustainability

Depending on the policies and procedures within a particular institution, such a business plan may also involve establishing a cost recovery plan and other strategies to assure the biobank's long-term sustainability. Although the discussion in this chapter has focused primarily on the financial aspects of biobanking economics, the major goal of developing a biobank business plan is to achieve long-term sustainability to mitigate fluctuations in funding and economic downturns that may affect research infrastructure. Sustainability has become a major topic for biobanks and has been incorporated into sessions at major biobank conferences such as ISBER and ESBB [18, 19]. The NCI Best Practices for Biospecimen Resources [12] includes in it Section C concerning custodianship Section C.1.2: Legacy or Contingency Plans:

> "Biospecimen resources' legacy or contingency plans should be part of the overall governance plan and should address the handling and disposition of biospecimens and associated data at one or more of the following points: (1) End of the budget period of the grant, (2) loss of management or termination of funding, (3) accomplishment of the specific research objectives of the study, (4) depletion of biospecimens, (5) achievement of critical data end points, and/or (6) discontinuation of participation by human research participants. At any of these points, an assessment of whether the stored biospecimens still have value for research should be conducted. If the stored biospecimens still have research value, the resource should consider whether to become financially self-sustaining. Alternatively, the resource should consider announcing the availability of the biospecimens for transfer to suitable research facilities by means appropriate for reaching a wide audience, if permitted by the informed consent document and the relevant IRB. Biospecimen resources should use the same decision-making criteria for allowing transfer of biospecimens to other biospecimen resources as they do when allowing transfer of biospecimens to investigators. The transfer of such biospecimens should be consistent with human subjects regulations, the informed consent under which the biospecimens and data were initially collected, and any other prior agreements and institutional policies that may apply."

This approach to custodianship of specimens and data is one approach to recommendations that can become part of a long-term sustainability plan. However it concentrates on managing collections which are in jeopardy through cost recovery and distribution plans. In their recent paper, Watson et al. [3] outlined a broader approach to sustainability. As mentioned in other parts of this chapter, biobanks are of a variety of sizes and purposes. Not all biobanks have the supporting infrastruc-

ture to develop comprehensive business plans involving cost recovery and other approaches outlined in this chapter. Watson et al. proposed that "biobank sustainability should be considered within a framework of three dimensions: financial, operational and social." In developing the CTRNet biobank certification program, the terms mono-, oligo- and poly-users were developed to describe the varying size and focus of biobanks [20]. In terms of sustainability these types of biobanks can differ greatly. For example, in considering the range of biobanks by the extent of the research use, smaller "mono" biobanks will usually have a narrow well-defined purpose and will often be self-sustaining for the duration of the focused grant or contract funding. Larger biobanks with diverse purposes where specimens may be collected for undetermined future use will usually find it more difficult to achieve complete cost recovery and long-term sustainability from outside funding sources.

The financial dimension of sustainability involves many of the points made elsewhere in this chapter: market strategy, customer focus, brand recognition and the accrual and user fee strategies. On the other hand, the operational and social dimensions provide additional complementary approaches that complete the picture of long-term biobank sustainability. The operational dimension is "where decisions are made that influence efficiency of either input, internal or output components of the biobanking process [5]." The social dimension encompasses interactions with stakeholders including the public, patient donors and other entities. This dimension includes publicity, workshops and similar efforts to establish lines of communication and involve stakeholders in the operation of the biobank. Another aspect of the social dimension involves establishing standards of biobank practice, which creates a measure of value of the biobank and its resources that will be advantageous as the biobank establishes itself as part of its sustainability initiative.

9 Conclusions

Much work needs to be done to better quantify the costs and benefits of standardizing biobank operations and economic effects of implementation of best practices, and approaches to long-term sustainability.

But progress is being made:

- Economic issues are beginning to be addressed in biobank best practices
- The competitive aspect integral to research and previously common in biobanking has begun to dissipate and biobank networks have been shown to enhance sustainability and economic effectiveness.
- Comprehensive cost analysis and recovery programs are being implemented and shared [21–24].
- New studies are being planned with consideration of costs and customers in mind.
- Biobank economics papers are appearing in the literature

- Examples of value and economic analyses are appearing e.g. the Moffitt-Merck Total Cancer Care Program [17].
- Sustainability has become a major topic at biobanking conferences, and is being addressed in the literature.

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Safety Issues in Biorepositories

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Abstract Biorepositories containing human and some animal tissues have many potential safety issues, especially biohazards and chemical hazards. In addition, other safety issues include physical, electrical and other hazards. Rarely, radiological safety may be an issue. In general, the extent of specific safety issues depends upon the goals and operations of the biorepository. The United States of America (USA) as well as other countries such as those of the European Union (EU) have regulations that cover a broad range of safety issues such as protection of employees from bloodborne pathogens and chemical hazards. Frequently, safety issues involving physical, electrical and fire safety are local (e.g., city) or regional (state or province). The goal of this chapter is to aid biorepositories in developing and improving their safety programs. In part, this is approached by informing biorepository personnel of sources of regulatory information and aids in developing a general safety program. Of note, this discussion is not sufficient to protect employees from safety hazards or to ensure an organization has an adequate safety program. Laboratory safety is continually evolving as new issues in safety arise and new approaches to protect individuals and the organization develop. Therefore, personnel and organizations must constantly review their approaches to safety.

Keywords Biorepository safety • Tissue banks • Human • Biohazards • Chemical • Physical safety • Fire • Electrical

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1 Introduction

Biorepositories have many potential safety hazards, especially chemical hazards and biological hazards; also, there are hazards involving fire and electrical safety as well as physical safety. The specific safety issues applicable to biorepositories depend upon the goals and operations of the biorepository. For example, because some biorepositories may specifically collect tissues from patients with bloodborne pathogens, biohazards may be a much more important issue for such biorepositories.

Some countries have safety regulations to protect laboratory employees. In the United States of American (USA), specific biorepository relevant regulations cover bloodborne pathogens, general laboratory chemicals and formaldehyde. Fire and electrical safety may follow guidelines of the National Fire Protection Association. Similar regulations concerning bloodborne and chemical hazards have been promulgated by the European Union (EU). In addition, safety regulations, especially involving physical, fire and electrical safety, may include regional (e.g., state or province) or local (e.g., city) regulations.

The goal of this chapter is to aid biorepositories in developing and improving their safety programs based on the experience of the Tissue Collection and Banking Facility (TCBF) of the University of Alabama at Birmingham (UAB) and of the authors. The information in this chapter ***is not adequate to ensure the safety of all biorepository personnel or to ensure that a laboratory is able to meet regulatory, certification and/or accreditation standards in safety***. However, this article provides a starting point which is not static in that there are new issues related to laboratory safety that frequently develop. For example, in the USA, requirements as to chemical safety are changing to make requirements more consistent with The Globally Harmonized System of the Classification and Labeling of Chemicals (GHS) of the World Health Organization (WHO) of the United Nations (UN). Aids in this transition include Hazard Communication Standards [1, 2], A Guide to the Globally Harmonized System of Classification and Labelling Chemicals [3] and the websites listed under chemical safety in Table 1.

Table 1 Resources on safety on the Internet

Website	Organization	Topics
Safety in general		
http://www.osha.gov	Occupational Safety and Health Administration, Department of Labor, USA	Current developmental and operational regulations; technical information; prevention information; training information; links to other sites
http://www.ccohs.ca/oshanswers	Canadian Centre for Occupational Health and Safety	Answers on frequently asked questions on safety
https://www.osha.europa.eu/en/legislation/index_html	Occupational and Health Administration, European Union	General safety, European Union

(continued)

Table 1 (continued)

Website	Organization	Topics
https://www.osha.europa	Occupational and Health Administration, European Union	General safety, European Union
http://www.rmlibrary.com/db/lawosha.htm	Libraries and Directories: Risk Management and Insurance Safety	Occupational safety laws of all 50 states of USA
http://www.cap.org	College of American Pathologists	General and technical information; laboratory management; laboratory safety
http://www.clsi.org/	Clinical and Laboratory Standards Institute (CLSI)	General and technical information; forms; safety; links
http://www.lbl.gov/ehs/pub3000	Lawrence Berkeley National Laboratory Health and Safety	Health and safety manual
http://www.healthsystem.virginia.edu/internet/epinet/	University of Virginia, International Health Care Worker Safety Center	Surveillance data
http://www.healthsystem.virginia.edu/internet/epinet/about_epinet.cfm	Exposure Prevention Information Network (EpiNet)	Surveillance data
https://www.osha.gov/dsg/hazcom/HCSFinalRegTxt.html	OSHA, USA	Safety aids
Biological safety		
http://www.cdc.gov	Centers for Disease Control and Prevention, Atlanta, GA	Surveillance data; prevention information; technical information; biohazards; links
http://www.absa.org	American Biological Safety Association (ABSA)	Technical information
http://www.cdc.gov/ncezid/	National Center for Emerging and Zoonotic Infectious Diseases	Combines the National Center for Infectious Disease and the National Center for Zoonotic, Vector-borne and Enteric Diseases
http://www.cdc.gov/nchhstp/	National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention (NCHHSTP)	Biological information on HIV/AIDS, Viral Hepatitis, STD, and TB Prevention
http://www.cdc.gov/ncird/	National Center for Immunization and Respiratory Diseases (NCIRD)	Biological information on Immunization and Respiratory Diseases
http://www.fda.gov/cber	Food and Drug Administration, Center for Biologics Evaluation and Research	Information on recalls, withdrawals, and safety issues concerning biologics
http://www.npic.orst.edu/	National Pesticide Information Center (NPIC)	Technical information on disinfectants; links to other sites
http://www.epa.gov/	Environmental Protection Agency	

(continued)

Table 1 (continued)

Website	Organization	Topics
http://www.defra.gov.uk/.	UK Department for Environment, Food and Rural Affairs (DEFRA)	Surveillance data on BSE in Europe; technical information on prions
http://www.cjd.ed.ac.uk	The National Creutzfeldt-Jakob Disease Surveillance Unit (NCJDSU)	Surveillance data on CJD; technical information on prions; links to other sites
http://www.who.int/csr/resources/publications/biosafety/WHO_CDS_CSR_LYO_2004_11/en/	WHO Laboratory Biosafety Manual	Biosafety information
Chemical safety		
https://www.osha.gov/dsg/hazcom/index/html	OSHA, USA	Frequently asked chemical safety questions
http://www.ccohs.ca/oshanswers/chemicals/ghs.html	Canadian Centre for Occupational Health and Safety	Chemical hazard questions
http://www.unece.org/trans/danger/publi/ghs/ghs_welcome_e.html	United Nations Economic Commission for Europe	Chemical safety
http://www.ghslegislation.com/asia-pacific/ghs-implementation-in-asia-pacific-countries-2/	GSH Legislation	Chemical regulation Asia-Pacific
http://www.cdc.gov/niosh/database.html	National Institute for Occupational Safety and Health (NIOSH)	Databases and information resource links and publications
http://www.ilo.org/public/english/protection/safework/cis/products/icsc/dtasht/index.htm	International Occupational Safety and Health Information Center (CIS)	Chemical data base; International Chemical Safety Cards (ICSC)
http://www.response.restoration.noaa.gov/chemaids/react.html	Office of Response and Restoration (OR&R)	Chemical reactivity worksheet; chemical database of reactivity of substances or mixture of substances
http://www.cdc.gov/niosh/chem-inx.html	Master Index of Occupational Health Guidelines for Chemical Hazards (NIOSH)	Guidelines for hazards of specific chemicals
http://www.who.int/ipcs/en/	WHO International Programme on Chemical Safety (IPCS)	Chemical safety information
http://www.who.int/ipcs/methods/harmonization/areas/ra_toolkit/en/	WHO Human Health Risk Assessment Toolkit: Chemical Hazards	Chemical safety information
Fire safety		
http://www.lbl.gov/ehs/pub3000/ch12.html	Lawrence Berkeley National Laboratory Health and Safety	Fire prevention and protection program
http://www.stonybrook.edu/ehs/fire/	Stony Brook University Environmental Health and Safety	Laboratory fire safety hazard assessment and work practices

(continued)

Table 1 (continued)

Website	Organization	Topics
http://www.nfpa.org	National Fire Protection Association	Codes and standards, safety information and training in fire prevention
Electrical safety		
http://www.lbl.gov/ehs/pub3000/CH14.html	Lawrence Berkeley National Laboratory Health and Safety	Electrical equipment safety program
http://web.princeton.edu/sites/ehs/labguide/sec_5.htm	Princeton University	Laboratory electrical safety program
http://www.ehs.uconn.edu/occ/elec.pdf	University of Connecticut Environmental Health and Safety	Electrical safety in the laboratory
http://www.nfpa.org	National Fire Protection Association	Electrical codes related to fire protection
Physical safety		
http://www.nfpa.org	National Fire Protection Association	Standards for storage of cryogenic fluids (NFPA.55 and NFPA.99)

2 Understanding Regulatory and Other Safety Issues Relevant to Biorepositories

Because there are extensive governmental regulations to protect the health and safety of employees of laboratories, there are numerous written guidelines from governmental and non-governmental organizations which can aid biorepositories in developing their safety programs. For example, web-based resources which may help in understanding the regulations in the USA, EU and other countries concerning safety are listed in Table 1. Also, review articles [4–8], the three editions of the Best Practices of the International Society of Biological and Environmental Repositories (ISBER) [9–11] and books (Table 2) may aid in developing a safety program for a biorepository. Biorepositories outside the USA will find many of these educational resources to be useful in developing their safety programs. Safety regulations and aids usually are written to aid academic, commercial and governmental laboratories, but these are relevant completely to biorepositories; thus, biorepositories can rely on these documents as aids in developing their safety programs. Of greatest use to biorepositories that are associated with medical facilities are the safety programs of the clinical and anatomic pathology laboratories of the associated medical facilities.

The goal of any safety program of a biorepository should be to minimize the chances of any injury of biorepository personnel as well as damage to the biorepository. To protect its personnel, a biorepository should follow a safety program which is usually a component of the safety program of the overall organization (e.g., a medical facility). Nevertheless, the biorepository safety program can be a separate, but dependent component of the overall safety program. For any organization, a safety committee develops and administers the safety program to monitor its effectiveness and to ensure the safety program is being followed. Because one of the goals

Table 2 Books on safety

Biosafety in the Laboratory: Prudent practices for the handling and disposal of infectious materials (1989) National Academies Press, Washington, DC
Block SS (2001) Disinfection, Sterilization, and Preservation, 5th ed. Lea and Febiger, Philadelphia, PA
Bloom BR (1994) Tuberculosis: Pathogenesis, Protection and Control. American Society for Microbiology Press, Washington, DC, pp. 85–110
Centers for Disease Control and Prevention/National Institutes of Health. (1999) Biosafety in Microbiological and Biomedical Laboratories, 4th ed. US Government Printing Office: US Department of Health and Human Services, Public Health Service, CDC and NIH, Washington, DC http://www.cdc.gov/biosafety/publications/bmbl5/BMBL.pdf
Fleming DO, Richardson JH, Tulis JJ, and Wesley D (1995) Laboratory Safety: Principles and Practices, 2nd edn. American Society for Microbiology Press, Washington, DC
Fredenburgh JL, Grizzle WE (1993) Safety and Compliance in the Histology Laboratory: Biohazards to Toxic Chemicals (available only at workshops)
Furr AK (2000) CRC Handbook of Laboratory Safety, 5th edn. CRC Press, Boca Raton, FL
Gile TJ (2010) Complete guide to laboratory safety, 3rd edn. HCPro, Inc., Marblehead, MA
Heinsohn PA, Jacobs RR, Concoby BA (1996) AIHA Biosafety Reference Manual, 2nd edn. American Industrial Hygiene Association, Fairfax, VA
Kent PT, Kubica GP (1985) Public Health Mycobacteriology. A Guide for the Level III Laboratory. US Department of Health and Human Services, Public Health Service, CDC, Atlanta, GA
Kubica GP, Dye WE (1967) Laboratory Methods for Clinical and Public Health Mycobacteriology. Public Health Service Publication, Number 1547. US Department of Health, Education, and Welfare. United States Government Printing Office, Washington, DC
Lieberman DF (1995) Biohazards Management Handbook. Marcel Dekker, New York
Fleming DO, Richardson JH, Tulis JI, Vesley D (1995) Laboratory Safety: Principles and Practices, 2nd edn. ASM Press (American Society for Microbiology), Washington, DC
Miller BM (1986) Laboratory Safety Principles and Practices. American Society for Microbiology, Washington, DC
OSHA QuickTakes (2012) A Guide to The Globally Harmonized System of Classification and Labelling of Chemicals, United States Department of Labor, Washington, DC https://www.osha.gov/dsg/hazcom/ghs.html
Padhye AA, Bennett JE, McGinnis MR, et al. (1998) Biosafety considerations in handling medically important fungi. Med Mycol 36:258–265
Preventing Occupational Disease and Injury (1991) American Public Health Association, Washington, DC
Richmond JY, Knudsen RC, Good RC (1996) Biosafety in the clinical mycobacteriology laboratory. Clin Lab Med 16:527–550
Richmond JY (1997) Designing a Modern Microbiological/Biomedical Laboratory: Lab Design and Process and Technology. American Biological Safety Association, Mundelein, IL
Richmond JY (2000a) Anthology of Biosafety I: Perspectives on Laboratory Design. American Biological Safety Association, Mundelein, IL
Richmond JY (2000b) Anthology of Biosafety II: Facility Design Considerations. American Biological Safety Association, Mundelein, IL
Richmond JY (2000c) Anthology of Biosafety III: Application of Principles. American Biological Safety Association, Mundelein, IL
Sewell DL (1995) Laboratory-associated infections and biosafety. Clin Microbiol Rev. 8:389–405
Wald PH, Stave G (2001) Physical and Biological Hazards of the Workplace, 2nd edn. Van Nostrand Reinhold, New York

of the safety program is to protect all the employees of the biorepository, each employee should work with their supervisor to provide input to the safety officer to aid in developing components of specific safety plans. Inputs of employees should be based on both their individual jobs and the areas in which they work. The safety plan will incorporate engineering needs such as correcting problems with ventilation, drainage, infrastructure, and space and will introduce engineering practices including the use of safety equipment in order to reduce the chances of injury to personnel or unnecessary exposure to hazards. There also should be emergency plans as, for example, when there is a large chemical spill. Safety programs also should include educational programs in safety, especially focusing on bloodborne pathogens, chemical hazards, formaldehyde and general issues in safety. Education of personnel also should include disposal of waste, including both biohazardous and chemical waste.

3 The Safety Infrastructure of a Biorepository

The Chief Executive Officer (CEO) of an organization typically appoints a safety committee which develops a safety program that covers the entire organization. A biorepository can use the safety committee and safety program of its parent organization, but also may have its specific safety issues covered by a subordinate safety committee, safety program and safety officer (SO). The safety committee develops, reviews, and changes, if necessary, the safety plan periodically; studies incidents and modifies the safety plan to prevent the recurrence of incidents; and supervises the safety officer. Of note, while the safety committee is responsible for overall safety, depending upon the country, the chief executive officer of the organization usually has the ultimate responsibility for safety. Sometimes this may involve criminal as well as civil liability.

The SO typically administers the safety plan, ensuring its implementation; the SO reviews and recommends appropriate changes to the safety program on an annual basis. This includes the review of training in safety, periodic monitoring of the use of safety equipment, monitoring the laboratory environment (e.g., ventilation, including vapor/fume exposure), confirmation of safe work practices, and evaluation of recommended health care (e.g., vaccinations for hepatitis B). The safety officer also documents safety incidents, studies their causes and recommends to the safety committee changes in the safety program to prevent the recurrence of specific incidents.

4 Training in Safety

Training in each specific area of safety (e.g., biohazards, especially bloodborne pathogens, laboratory chemical hazards and formaldehyde) follows the same general approach and frequently has the same general requirements for each area of safety.

Each employee should be given appropriate training before the employee begins work in the biorepository and/or before new duties are assumed by the employee in which safety issues are different and/or new working areas are assigned. The trainers must be knowledgeable in safety, and training should be at an appropriate educational level and language for each employee. The training also should be commensurate with the risks to which the employee may be exposed (e.g., for biorepositories not using or storing chemicals, no training in chemical safety may be required). Thus, different levels of training in safety should be selected based on the goals and operations of the biorepository and on the needs of each employee. Of note, janitorial or secretarial employees might not perform risky tasks, yet they may be exposed to a risky environment. Specifically, janitorial personnel must be trained concerning safety issues associated with the areas they clean and secretarial personnel should be aware that "papers" or portable equipment (e.g., laptops, tablets) from the biorepository laboratory may be contaminated with biohazardous or chemical agents.

The training of each employee should be updated periodically according to governmental regulations and/or the needs of the employee. Regulations in the USA require that employees be trained in specific areas of safety affecting their activities (e.g., laboratory safety, chemical hazards, bloodborne pathogens and formaldehyde), the training should be documented and updated annually, and in the USA, the records of training should be kept for at least 3 years. The safety officer should audit the required training of each employee, ensure deficits in training are corrected, and record the audits in the quality management system (QMS) records as aspects of the safety program.

5 Biorepository Safety Areas

5.1 Biohazards

Biorepositories typically collect, process, store, and distribute human and/or animal tissues. Because all human tissues and some animal tissues may contain organisms that are potentially infectious to humans, all human tissues and some animal tissues (e.g., tissue products such as blood from some primates such as Macaque monkeys) should be treated with universal precautions (e.g., all human tissues and/or their derivatives are treated as potentially infectious to man). Biorepositories typically need an extensive plan to minimize exposure to and prevent injury from infectious agents. Of note, some animal tissues may be dangerous to humans such as tissues infected with mad cow disease or deer-elk wasting disease, both secondary to prions, tissues from animal models of human infectious diseases, and tissues from some primates.

Some countries and regions of countries (e.g., provinces, states) have regulations as to biosafety. In the USA and EU, there are specific regulatory requirements aimed at preventing exposure to bloodborne pathogens for organizations in which employees come into contact with human and some animal tissues or their derivatives (29CFR1910.1030 and directives 2000/54/EC and 2010/32/EC respectively).

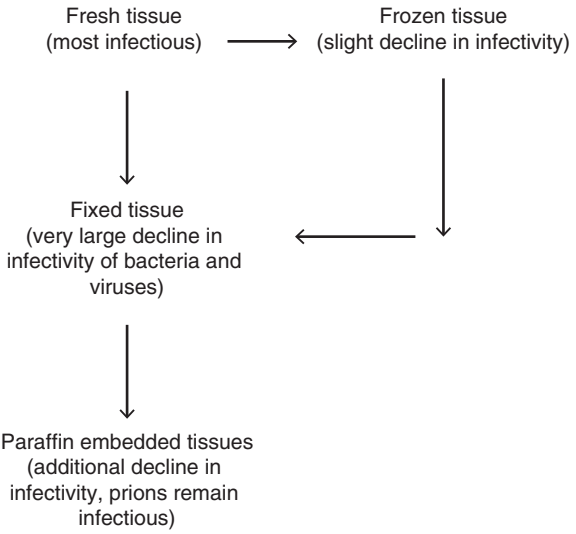

Fig. 1 Effects of tissue processing on the potential infection

Thus, for such organizations, including many biorepositories, there must be a safety program that minimizes the chance of infection with bloodborne pathogens. Bloodborne pathogens include human immunodeficiency virus (HIV) and related viruses, hepatitis viruses such as hepatitis B and C and D and the hemorrhagic fever viruses such as hantavirus, Ebola virus and related viruses. Of note, fresh tissues are the most infectious and the danger declines upon the various steps of tissue processing (Fig. 1). The greatest decline occurs on fixation; however, even paraffin blocks have infectious risks due to prions.

A safety program requires universal precautions to prevent exposure to bloodborne pathogens because of contact with any human tissues or animal models of human infectious diseases. In the USA, a training program focusing on bloodborne pathogens is required for all personnel who may come in contact with human tissues. The training program should include information about how bloodborne and other pathogens are transmitted and cause diseases. This training program, including yearly updates, must be documented for everyone in contact with human tissues or potentially infectious animal tissues (see Sect. 4). Of concern, there are multiple non-bloodborne pathogens such as tuberculosis which are very dangerous and infectious and which, in the USA and some other countries, may not specifically be regulated; however, all dangerous organisms should be addressed in any effective safety program.

When contacting human tissues, including bodily fluids, engineering practices should be used to protect personnel from exposures and hence infections. This includes the required use of appropriate safety equipment. The specific safety equipment should be specified in the standard operating procedures (SOPs) of each task. Such equipment includes laboratory coats, appropriate gloves, safety glasses and masks as well as approaches such as protective containers to prevent sticks/cuts from any material that could cause breaks in the skin (sharps) including needles.

The type of laboratory safety equipment should vary as the extent of potential contact increases. For example, exposures to small (e.g., 10 mL) tubes of blood require less safety equipment than exposure to large volumes of blood such as during an autopsy. In the first case, a laboratory coat, gloves, safety glasses and a mask may be sufficient to prevent exposure of skin and personal clothing, but during an autopsy, usually surgical masks and scrubs, aprons and more extensive barriers are necessary to prevent exposures to skin, mucous membranes and personal clothing. Similarly, surgical quality gloves should be used instead of lower quality latex gloves because of potential exposures to bone shards and cutting equipment (scalpels and saws) which may increase the likelihood of infections via cuts and tears in gloves. In addition, during autopsies there should be increased protection of eyes and other mucous membranes which are pathways of exposure to pathogens.

Universal precautions should always be followed; however, tissues from patients known to be infected with bloodborne pathogens, tuberculosis, other atypical bacteria (e.g., leprosy) and antibiotic resistant bacteria should be of special concern to personnel. In such cases, some biorepositories, including the TCBF, may elect not to collect and store such tissue to protect not only their personnel but also the personnel of laboratories to which such tissue may be distributed. Also, in most cases investigators will not accept such tissues. Of note, it has been the experience of the TCBF at UAB that sometimes the personnel of laboratories to which biorepositories distribute tissues are not adequately trained in biosafety. Thus, it is recommended as part of the biorepository agreement or material transfer agreement (MTA) with the recipient institution, that the personnel of organizations/laboratories receiving tissues be appropriately trained in biosafety. Also, it is appropriate to add an indemnification clause to the biorepository agreement or MTA to protect legally the biorepository due to injury of personnel at the recipient institution. There are multiple training programs in biohazards available on the web that can be identified using search engines.

Biorepositories must be aware there are special national and international requirements for transfer of human tissues and their derivatives, animal tissues and infectious agents between organizations and across borders. For example, the International Air Transport Association (IATA) has shipping requirements and required training in shipping. The regulations of IATA and its training requirements cover biohazards as well as chemical hazards.

5.2 Chemical Hazards

Most chemicals used in biorepositories potentially have some health effects depending upon the modes of contact and the extent of exposure. Chemicals can have multiple health hazards, and may be toxic, irritants, allergens, carcinogens, and/or teratogens. In addition, some chemicals may be flammable and thus, fire hazards

(e.g., xylene, alcohols and acetone) and/or explosive risks as discussed in Sect. 5.4. Contact with chemicals may be via the skin or mucous membranes (e.g., eyes, nose, and mouth), vapors/fumes, or ingestion. Each mode of exposure has different types and extents of toxicity. For example, exposure of the skin to formaldehyde based fixatives may induce irritations and/or allergic reactions, inhalation of formaldehyde vapors may have carcinogenic activity in addition to irritations and/or allergic reactions, and ingestion of formaldehyde can be toxic.

To protect personnel, a component of the safety program should be devoted specifically to chemical safety including formaldehyde-based chemicals. As discussed under the training section, the chemical safety plan should include training in chemical safety for all biorepository employees who have contact with chemicals and/or, the space in which chemicals are used and/or stored. Also records leaving the laboratory (e.g., paper or portable devices such as laptops, smart phones, or tablets) should be treated as potentially contaminated with chemicals.

The World Health Organization (WHO), a special agency of the United Nations (UN), has developed multiple components of a chemical safety plan and has newly implemented The Globally Harmonized System of the Classification and Labeling of Chemicals (GHS). The GHS requirements for labeling chemical containers consist of six major elements: product identifier, supplier identification, signal words, hazardous statements, precautionary statements and pictograms. The explanation of the major elements are as follows:

- Product Identifier: the product name and code (catalog number);
- Supplier Identification: manufacture or supplier name, street address, city, state, postal code and country;
- Signal Word: one of two words used to alert the user of the relative level of hazard severity of the product, “Danger” and “Warning.” Danger is used for the more severe hazard categories. Only one signal word can be used on a chemical label to indicate the severity of hazard;
- Hazard Statements: phrases assigned to hazard classes and categories that describe the nature of a hazardous product, including when appropriate, the degree of the hazard. The specific wording of a hazardous statement is dependent on the hazard classification. Examples of hazards statements are “Causes eye irritation”; “Toxic if swallowed”; “Flammable liquid and vapor”;
- Precautionary Statements: Phrases that describe recommended measures that should be taken to minimize or prevent adverse effects resulting from exposure to a hazardous chemical. The statement may cover topics related to personal protection, storage and disposal. Examples of precautionary statements are “wear eye/face protection”, “store in well-ventilated place”, “if on skin, wash with plenty of water”, “dispose of contents….”
- Pictograms: GHS has developed specific standard pictograms used in expressing chemical hazards. Figure 2 demonstrates the standard GHS pictograms used in labeling of chemical containers and in safety data sheets (SDS) with explanations. A group of similar pictograms with different colors and different subcategories are used to indicate chemical hazards in transportation.

Pictogram	Description	Chemical Hazards
	Flame over circle	Oxidizer
	Flame	Flammables / Self-reactive chemicals; Emits Flammable gas; Organic Peroxides
	Exploding Bomb	Explosive; Self-reactive; Organic peroxides
	Skull and Crossbones	Acute Toxicity (severe)
	Corrosion (metal or skin)	Corrosive
	Gas Cylinder	Gases under pressure
	Health Hazard	Carcinogen /Mutagenicity; Respiratory sensitizer; Target organ toxicity (acute and chronic); Aspiration toxicity
	Exclamation mark	Acute toxicity; severe responses; target organ toxicity on a single exposure

Fig. 2 Chemical hazard pictograms (container labels and SDS)

A safety data sheet serves as a workplace hazard warning, provides information to prevent direct exposures to a chemical and specifies actions upon exposure to a specific chemical. As of June 1, 2015, “The Hazard Communication Standard (HCS) of the USA” requires chemical manufacturers, distributors, or importers to provide users with SDS (formerly known as material safety data sheets or MSDSs) in order to communicate in a uniform format the hazards of each hazardous chemical provided. The information contained in the new GHS format for the SDS is basically the same as the MSDS, except the SDSs have a mandated, consistent and user-friendly, 16-section format. Sections 1–8 contain information in reference to chemical and provider identification, hazards, composition, first aid measures, fire-fighting measures, accidental release requirements (spills and leaks), proper handling and storage and exposure controls and personal protection information. Sections 9 through 11 contain technical and scientific information, physical and chemical properties, stability and reactivity, and toxicological information. Sections 12–15 contain ecological information, disposal considerations, transport information and regulatory information. Section 16 with “Other Information” is a general section that may include the date of SDS preparation, last revision and any

other pertinent information. Thus SDSs inform users of the hazards of each chemical, required personnel protection, emergency actions on exposure, emergency contact information, and technical information that may affect the uses, storage, transport and disposal of the chemical.

Each chemical that is commercially purchased has a SDS that must be readily available to all employees who could come into contact with the specific chemical. The SDS is prepared by the manufacturer or company that has modified the chemical (e.g., repackaging) and is available from that company. As described, the SDS includes the hazards of the specific chemical (e.g., toxicity), required personnel protection, procedures to minimize toxic exposures, emergency actions on exposure, emergency contact information so that additional information on the hazards of the chemical and potential treatments of exposure can be obtained rapidly and technical information that may affect the uses, storage, transport and disposal of the chemical.

Biorepositories outside the USA may be under different regulations; nevertheless, the laws of the USA and EU may provide aids in developing a chemical safety program. Also, SDS are now international and understanding SDS is an important component of any laboratory safety plan.

While the hazards of chemicals are specified in SDS, combinations of chemicals used in the laboratory may have hazards that are unknown and may be beyond the hazards of the individual chemical components. Also, combining chemicals in the laboratory may require special precautions. It may be obvious that concentrated strong acids (e.g., hydrochloric acid) should never be combined directly with strong bases (e.g., sodium hydroxide) without dilution and extreme care; however, mixing strong oxidizers (e.g., potassium permanganate) with materials with high carbon content (e.g. ethylene glycol) may cause spontaneous fires. The hazards of such mixing may be unrecognized and should be approached with great care. These are just a few of the examples which should be included in the educational program in chemical safety.

As with biohazards, each employee should have input into the chemical safety plan that affects him/her based on the chemicals used and the chemicals present in the space in which work is performed. The GHS has already had a large impact on the training in chemical hazards required in the USA, in that there will be additional training in the new mandated formats for labeling of chemicals and of SDSs.

To protect biorepository personnel from chemical hazards requires engineering practices including safety equipment. The goal of these engineering practices is to prevent chemical exposures that may cause injury to personnel and/or damage to the biorepository. Because of the varying toxicities among chemicals, effective engineering practices vary with each chemical.

General safety practices should prevent the chemical exposures of skin, personal clothing, oral and other mucous membranes (e.g., eyes), lungs via fumes/vapors or oral ingestion (e.g., no oral pipetting). For less toxic chemicals, safety equipment includes a laboratory coat, safety glasses, a mask, appropriate chemically resistant gloves, access to eye washes and a shower and fire extinguisher. Note, latex gloves are not appropriate protection against chemical exposure.

Chemicals, especially flammable chemicals and caustic agents, should be stored in certified chemical storage cabinets. However, storage of large quantities of flammables should be minimized; similarly, strong acids and strong bases should not be stored together. Also, the flammable storage cabinet should not be positioned at the entrance/exit of a space. For more toxic chemicals and chemicals with dangerous vapors, more intensive engineering practices may be required, including appropriate changes in ventilation and drainage.

There are requirements and regulations related to chemical safety in the USA and some other countries (EU) that are likely to affect biorepositories. In the USA, these include Occupational Exposure to Hazardous Chemicals in Laboratories (29 CFR 1910.1450), the Hazard Communication Standard (29 CFR 1910.1200), and the Formaldehyde Standard (29 CFR 1910.1048). There are similar requirements in the EU that also are applicable to biorepositories. European health and safety requirements for laboratories are regulated by individual directives, of which the most important are: OSHA Europa 94/24/EE, which sets minimum requirements for the protection of workers exposed to chemical agents in the workplace. 2004/37/EEC protects workers from the risks related to exposure to carcinogens and mutagens at work. 91/322/EEC, 96/94/EC, 2000/39/EC and 2006/15/EC establish occupational exposure limits for the EU, and 92/58/EEC contains the regulations on classification and labeling of chemicals and provides important information concerning safety labels of chemical containers and safety data sheets.

In addition, if tissue specimens are shipped via national or international air transport, there are requirements for chemical safety and training that are required by the International Air Transport Association.

In the USA, the Occupational Exposure to Hazardous Chemicals in Laboratories (The Laboratory Standard) requires that employers develop a written chemical safety (hygiene) plan. The chemical safety plan for a biorepository must be able to protect all employees from hazardous chemicals. Specifically, the chemical safety plan should maintain chemical exposures below the action level or in its absence, the permissible exposure limit (PEL) for each specific chemical. Biorepository safety plans also should clarify and incorporate, if appropriate, the Formaldehyde Standard, especially if the biorepository repackages or prepares formaldehyde solutions and provides them outside the biorepository.

The minimum required elements of a chemical safety plan should include the following:

1. Plans for developing and implementing the chemical safety plan and monitoring its utilization and effectiveness.
2. Plans for monitoring the exposures of employees or visitors to hazardous chemicals, reporting, and documenting chemical safety incidents and modifying the safety plan to prevent recurrence.
3. An effective training program for all individuals working with chemicals or in areas where chemicals are used or stored.
4. A written emergency plan to address chemical spills. The plan should incorporate prevention, containment, clean-up and waste disposal including contaminated materials used in the clean-up. Also, there should be approaches to minimize personnel exposed during clean-up.

5. A policy to minimize exposure to hazardous fumes which includes minimizing inhalation by personnel, monitoring of the effectiveness of ventilation of any space where volatile chemicals are used or stored and planning for ventilation failures.
6. A policy which includes minimizing exposures of skin, eyes, mucous membrane, and personal clothing to chemicals and washing of hands and exposed skin after use and/or exposure to hazardous chemicals.
7. Plans for emergency evacuation and medical care for employees injured by hazardous chemicals and safety drills for chemical emergencies.
8. Policies prohibiting eating, drinking, smoking, gum chewing, application of cosmetics in the laboratory and storing food and/or beverages in laboratory storage areas, laboratory refrigerators and freezers.
9. A policy requiring protection of personnel and visitors from chemical exposures. This includes wearing appropriate protective equipment including laboratory coats, suitable gloves, eye and mucous membrane protection when there is a potential for contact with toxic chemicals. Gloves should be appropriate for chemical protection and should be inspected before using and washed before removing. Mouth pipetting and mouth suctioning for starting a siphon must be prohibited. The use of contact lenses in the laboratory should be avoided.
10. A policy to document and observe chemical exposure limits if established and to follow legal requirements for specific hazardous chemicals. Employees should be knowledgeable of these issues.

Most biorepositories have relatively moderate amounts of chemicals; however, using even very small amounts of specific chemicals may be dangerous. For example, dry picric acid (used in some histochemical stains) constitutes an explosive hazard. Combinations of chemicals also may have different safety profiles including spontaneous combustion or accelerated heating which could cause splashing and boiling. Personnel should minimize direct contact with even small quantities of carcinogens, teratogens, and/or highly toxic agents.

Hospital safety programs related to their laboratories usually address uses of most chemicals within a biorepository. SOPs should include precautions for specific chemical uses. The following approaches are applicable to chemical solutions prepared for specific uses:

- All solutions made in the laboratory must be labeled and include the ingredients and hazards as well as the date prepared and an expiration date. Combinations of chemicals should include the SDS for each component chemical. In addition, the biorepository must assume the combined chemicals are more hazardous than the sum of the toxicities of the individual chemical components.
- The composition of any chemical substance produced by the biorepository exclusively for its use requires the biorepository to prepare a SDS for its personnel and if the substance is hazardous, the biorepository must provide appropriate training.
- If a chemical substance is produced or repackaged by the biorepository for an outside site, the biorepository is required to prepare a SDS for the other site(s) which includes the new GHS labeling requirements.

- Because many chemicals have some hazards, chemical exposures should be minimized and universal precautions for handling all chemicals should be utilized. More hazardous chemicals in the biorepository will require specific guidelines. Prudent approaches include the following:
  - Follow the chemical safety plan.
  - Contact with chemicals should be avoided and chemicals should be washed quickly from exposed sites.
  - Use appropriate safety equipment (e.g., laboratory coat, safety glasses, mask, gloves) to minimize exposure to hazardous chemicals.
  - Minimize exposure to chemicals with no known significant hazard.
  - Take special precautions with chemicals that present moderate or severe hazards.
  - Assume that any mixture of chemicals will be more toxic than its most toxic component.
  - Take care during maintenance of equipment and contact with surfaces potentially contaminated with hazardous chemicals.

When biorepositories work with chemicals, the chemical safety plan should ensure that potential injuries are avoided by proper SOPs which identify required safety equipment as well as by extensive education of each employee. Such approaches to chemical safety are regulated in the USA by the Occupational Safety and Health Administration (OSHA) of the Department of Labor. Of note, in the USA OSHA can inspect biorepositories and impose large fines for safety violations.

Several potential hazardous chemicals are common to biorepositories, especially biorepositories which have histology laboratories as a component for providing quality control examinations and specialty specimens for research (e.g., paraffin blocks). These chemicals include formaldehyde, which is the most common type of fixative used in the preparation of paraffin blocks. Formaldehyde is an irritant and allergen, is toxic and is a carcinogen. Because formaldehyde is very commonly used in many products such as furniture and carpets, a severe allergy to formaldehyde is very debilitating. In the USA, there is a special law that addresses chemicals containing formaldehyde (the Formaldehyde Standard 29 CFR 1910.1450). This law has specific safety requirements for the preparation and use of chemical solutions containing formaldehyde.

Xylene, acetone and alcohols also may be used in biorepositories; these are chemical hazards especially due to their flammable vapors and to their toxicity; employees should minimize exposures to all chemicals. Hazards of all chemicals must be documented on their chemical containers. SDSs must be readily available to personnel in the biorepository for every chemical used, present or stored in the biorepository and employees should minimize exposures to all chemicals.

5.3 Physical Security and Safety

Physical hazards may be common in specific biorepositories; thus, the physical safety of employees is an important safety issue. Physical safety incorporates a wide range of concerns from ensuring that employees are not physically injured by

others, to preventing falls. Approaches to ensuring physical safety include control of and quality of the overall infrastructure (e.g., facilities) of the biorepository. Damaged steps and rugs, slippery floors and inappropriate use of furniture and equipment may lead to injuries of employees. Recently, new standards for areas of health care facilities which store liquid nitrogen and other cryogenic fluids have been developed by the National Fire Protection Association. These include NFPA.55 and NFPA.99. These new standards may affect the design and/or infrastructure of biorepositories. Biorepositories should check these requirements with their associated organizational health and safety group or safety committee.

Examples of poor compliance with physical safety include use of chairs as ladders, slippery floors contaminated by paraffin and soaps/fluids, and file cabinets, cylinders and shelves that are inadequately secured; all these problems can lead to injuries. Unsecured equipment, files and cabinets are especially dangerous during earthquakes. Other potential physical injuries include injuries to the back secondary to lifting (e.g., racks from liquid nitrogen freezers), repetitive action injuries, and burns both hot and cold (e.g., from dry ice and liquid nitrogen). The potential for each of these types of injuries should be evaluated for each employee and a protection plan should be a component of the overall safety plan.

Physical injuries that are more difficult to avoid include minor cuts (e.g., paper) and minor injuries secondary to inattention. Of importance, minor injuries should not be exacerbated by exposure of broken skin to toxic chemicals or biohazards. The safety program should incorporate engineering practices to minimize physical injury. For example, the cause of cold and hot burns can be ameliorated by the use of thermal protective gloves to protect against high and low temperatures. Such issues should be addressed in the overall safety program and in SOPs of each task.

Overall security of the biorepository requires limiting or preventing access by unauthorized personnel. Also, threats to employees, especially by other employees, should not be tolerated. Of note, the protection of the employees' safety may extend outside the biorepository to emergency exits and pathways and areas surrounding the workplace, including parking areas.

5.4 Fire Safety

Biorepositories may utilize and store chemicals that may be fire hazards, such as xylene, acetone and ethanol. Thus, fire safety should be of concern to such biorepositories. The goal of the fire safety program should be to facilitate personnel rapidly escaping from fires and other emergencies; thus, clear emergency exit pathways should be posted at the exits of all rooms as well as general areas of the biorepository. The emergency exits should be described in the safety training program. Emergency exits should never be blocked, obstructed or locked; hallways should not be cluttered or obstructed. Similarly, access to fire blankets, showers, and fire equipment must not be impeded. Fire equipment (e.g., showers, fire extinguishers) should be tested periodically and results documented. There should be periodic fire drills to ensure that emergency exits are known and accessible. Flammable chemicals should be stored appropriately in chemical safety cabinets.

The volume of flammable agents stored in each cabinet should not exceed the cabinet's protective standard and the total amount stored in biorepositories should be appropriate and may be regulated locally and/or by accreditation/certification agencies.

Smoking should be prohibited in the biorepository. Furniture, rugs, and equipment should meet fire retardant standards. Similarly, doors that serve as barriers to fire should meet the requirements for construction of buildings that house laboratories such as biorepositories. In the USA, aids to minimize fire hazards are available from the National Fire Association (NFA). One approach to evaluating fire safety issues is by inviting an inspection by the local fire department.

5.5 Electrical Safety

All equipment of the biorepository must be electrically grounded and the grounding should be tested for each piece of equipment when it is put into operation and yearly thereafter. Electrical base plugs must also be grounded (testing documented) and also should be in good working condition. All work on the electrical system should be approached with great care by certified electricians who should ensure that all electrical working areas are protected by removal or inactivation of fuses; there should be written warnings at the fuse box to prevent activation while electrical work is in progress.

Each site should decide whether or not personal electrical devices can be brought into the biorepository. If permitted, electrical appliances such as radios should not be inadvertently ignored when testing biorepository equipment for grounding. In addition, personnel should be very careful with electrical appliances/equipment around water, especially bathrooms/showers and sinks.

6 Conclusions

The safe operation of a biorepository requires that all employees work toward maintaining a safe working environment. All employees of the biorepository need to contribute to developing and monitoring of an effective safety program. The infrastructure of the biorepository should be monitored by the safety officer and problems corrected rapidly; training of all personnel as to the safety hazards should be appropriate for special types of biorepository operations including protecting against biohazards, chemical hazards and physical hazards, should be updated yearly and should be documented. Also, biorepositories should identify and monitor electrical and fire hazards. The safety plan should use engineering practices to aid in ensuring a safe working environment. This includes the use of safety equipment such as laboratory coats, safety glasses, masks, and appropriate gloves as well as good ventilation and drainage of the site. The safety plan should be dynamic and

carefully evaluated, with annual reviews and changes necessary to minimize the recurrence of all safety incidents which should be carefully evaluated. Of note, a safe working environment should be established so that each employee focuses on protecting the health of himself as well as of other employees.

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Biobanks as Producers of Reference Materials

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Abstract As diagnostics and clinical research increase in complexity and interdependency, there is an increasing need in the diagnostic and pharmaceutical industries for formal certification of clinical biospecimens for nominal properties, so as to be considered Reference Materials. Certified clinical biospecimens that are collected, processed, characterized, stored and distributed by biobanks will facilitate diagnostic test development, evaluation and quality assurance, raising and harmonizing the standards of regulatory submissions based on clinical biospecimen analysis. For clinical biospecimens, certification relates to qualitative and/or quantitative characteristics of diagnosis (clinical, biological and pathological). For certification, biospecimen purity, characterization, fitness-for-purpose, homogeneity and stability, must be evaluated and thoroughly documented. Much of this data is currently collected by biobanks, however formal requirements are needed and biobanks themselves should be accredited to attribute reference material status by adhering to ISO 17034 requirements. This chapter describes potential biospecimen certification, and illustrates the certification process with some examples, which have been published in Biopreservation and Biobanking 2014; 12:113–120.

Keywords Biobank • Biospecimen • Certification • Characterization • Fit-for-purpose • ISO Guide 34 • Nominal value • Processing • Reference material • Purity • Stability

1 Background

Certification of a reference material—a substance, which is accurately and precisely characterized, and established as fit for its intended use in a measurement process—is essential for providing a guarantee of the quality, authenticity and content of the material. In the clinical diagnostics and research industries, as the use of biospecimens takes on an increasingly important role, there is an undeniable growing need

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to establish reference materials (RMs) or certified reference materials (CRMs) in this field. Biospecimens such as blood, urine, tissues, saliva, cerebrospinal fluid, stool, hair and cell lines, are analyzed for potential prognostic, predictive and diagnostic markers in order to make diagnoses and evaluate the impact of treatments on various biologic targets.

Certification of biobanks is currently performed to ISO9001 standards. For producers of reference materials, certification of materials requires adherence to the ISO 17034 requirements [1] which address production planning, homogeneity and stability testing, and value assignment, calculation of the total uncertainty of the assigned value, certificate issue, and post-distribution service. Nonetheless in the case of biospecimens, available certification guidelines have not kept pace with the rapid evolution in this domain. The development of established procedures to certify biospecimens—how they are acquired, validated, processed, stored and distributed—has become a critical issue, notably with respect to diagnostic tests. A prime example is seen in the *in vitro* diagnostic industry, with increasingly demanding regulatory requirements for qualified biospecimens [2, 3].

For clinical biospecimens, the challenge for certification lies in the fact that it relies on the characteristics of diagnosis (clinical, biological and pathological), which are often qualitative. Characterization concerns both the original case from which the specimen was obtained from (in which diagnosis is based on clinical, biological or histopathological characteristics) and the biospecimen itself (molecular and cellular characteristics). In the context of certifying biospecimens for a clinical qualitative property, application of ISO 17034 to biospecimens thus implies a fundamental shift in focus from chemical substance purity to diagnostic accuracy and related biospecimen characterization.

Biospecimen "annotations" contain patient-related clinical and biological data as well as information on specimen-related processing (or preanalytical procedures). These annotations are used to ensure the reliability of research results. Relevant annotations may include information obtained from a different paired specimen which can be used to confirm the biospecimen origin. Essential preanalytical variables were recently defined according to biospecimen type and their reporting was standardized [4–7]. Accurate clinical, biological and anatomopathological annotations, as well as precise preanalytical records will help to avoid artifactual biomarkers and false positive results [8].

Definition of a biospecimen as a RM requires accurate data on processing, purity, characterization, fitness-for-purpose, homogeneity and stability. This chapter reviews these elements in the context of establishing certification of clinical biospecimens as RMs, according to ISO 17034 [1, 9]. The specific elements that need to be documented and processes performed will vary depending on the nature of the specimen and the downstream applications. To illustrate this, we have applied these requirements to four examples of clinical specimens; two are "simple" samples (serum, CSF) and two are more complex derivatives (DNA extracted from tissue, tissue-derived cell line).

2 Certification Procedures

2.1 Purity Assessment

Purity—a measure of the absence of "contamination"—is important to limit false negatives, due to inhibition of a chemical reaction, or false positives, due to interference in the reaction, and ensure the accuracy of measurements made with the material. Purity measures vary depending on the specimen type and the downstream application. Factors to take into consideration include the presence of related entities with the potential for cross-reactions (proteins, antibodies, etc.), inappropriate materials such as blood contamination in non-blood fluids, or absence of microbial contamination (bacteria, yeast, fungi, virus) in cell lines.

2.2 Biospecimen Value Assignment and Characterization

Certification involves characterizing the biospecimen and concerns the attribution of a property value which generally requires proof of diagnosis (clinical, molecular, histopathological evidence), or cellular characterization (*in vitro*, *in vivo* and genetic profile), as appropriate. Complementary characterization can include related data such as gender, age, ethnicity, medication intake at the time of specimen collection, supportive clinical evaluations, confirmation of patient origin of the biospecimen (e.g., by paired sample genetic analysis) and genetic, proteomic and metabolomic profiles is also important.

2.3 Fit-for-Purpose Study

A sample that is fit-for-purpose is one which is considered adequate for selected downstream analysis. Certification of a clinical biospecimen as reference material must include description of the scope of its intended utilization, but also of excluded utilizations (e.g. fit for proteomic but not for metabolomics analyses).

2.4 Homogeneity Evaluation

Homogeneity is evaluated to ensure that all aliquots of a sample are similarly representative of the clinical condition. Nonetheless this can be difficult to evaluate in some cases; for example, cell lines may be subject to genetic drift and the presence of different cell sub-types, which are difficult to quantify; slides from an FFPE block have poor homogeneity due to inherent tissue heterogeneity.

2.5 Stability Study

Short and long-term stability studies should be performed to determine the extent of potential degradation and overall integrity of the material for use in downstream applications such as assays (enzymatic reactions, sequencing, proteomics, gene expression, etc.). Short-term stability studies focus on specimen transport, whereas long-term stability studies focus on specimen storage.

Both homogeneity and stability conclusions are based on the ISO Guide 35 Reference materials-Guidance for the characterization and the assessment of the homogeneity and stability of the material (*in preparation*).

2.6 Documentation of Material Processing

Documentation of applied procedures is a critical part of certification in any clinical diagnostic and research context. In the same way that assays performed on a biospecimen, downstream of collection, are precisely recorded, equivalent information must be available for the biospecimen origin and processing procedures to ensure the validity of the downstream outcomes. Documentation must be implemented routinely, rigorously and throughout the collection and processing procedure, ideally, with a computerized system.

A non-exhaustive list of elements to be included in the documentation trail includes the source of the biospecimen, where and when it was collected, relevant information about the source (e.g. gender, treatments, allowing for the potential need for confidentiality and informed consent), body/tissue location and specimen type, references for the tools used to collect specimens (needle, syringe and container), conditions of collection (timing, temperature, media used) and transportation.

Any processing procedures must be noted. This includes physical treatments, e.g. centrifugation conditions (speed, time, temperature, brake speed), as well as chemical treatments, e.g. any materials added to the sample (enzymes, chemicals), and aliquoting procedures. For tissues and cell lines which are cultured, culture methods (protocols, including enzymes, chemicals or kits), and batch and cell passage numbers must be documented. Protocols used for any assays performed for sample characterization must be noted.

Storage conditions must be recorded (freezing protocol, temperature, container, freeze/thaw cycles, biorepository). Time intervals between collection, processing and storage, as well as any precautions taken to minimize contamination of samples must also be available. Finally, accreditation details of testing laboratories having performed assays for the reference material characterization must be documented.

3 Application of Certification Procedures to Four Potential RM Biospecimens

3.1 Serum from Acute Chlamydia trachomatis Infection

C. trachomatis is a sexually transmitted bacterial pathogen which can result in serious reproductive complications including pelvic inflammatory disease, ectopic pregnancies and tubal infertility. Serologic diagnostic tests are important in measuring past and current infection status in women treated at infertility clinics. Serum samples can be used for the development and validation of serological diagnostic kits. Assessment of the performance of a serological assay for *Chlamydia* infection is based on analysis of serum samples collected from infected patients and the potential certification process for using serum as a reference material is discussed below.

Purity: Contact with other chlamydial species, such as *Chlamydophila pneumoniae* may confound interpretation of serum antibody results due to potential cross-reactions with common chlamydial antigens. Thorough characterization of the serum samples in terms of antibodies specific to other chlamydial species is performed with serologic assays based on recombinant antigens from the different species [10].

Value assignment and characterization: To certify the presence of acute infection, direct diagnosis of *C. trachomatis* in a paired urogenital specimen such as a urine specimen or a urethral/cervical swab must be performed by an accredited laboratory. Nucleic acid amplifications tests (NAATs) have replaced culturing as the reference method for direct laboratory diagnosis of *C. trachomatis*. NAATs include PCR, ligase chain reaction, strand displacement amplification or transcription mediated amplification. Once assigned to the urogenital specimen, this property value is assigned by extension to the paired serum specimen. Stringent negative controls should be included in the NAATs to avoid false positive results. Positive results from one NAAT should be confirmed using another NAAT or with the same NAAT targeting a different gene [11]. If only one NAAT is available, and has x% specificity, then the uncertainty of the material characterization is considered $(100 - x)\%$. Diagnosis can also be performed by direct antigen tests, based on smear immunofluorescence. For past genital chlamydial infection, it is important that an assay containing antigens or whole elementary bodies of different species of *Chlamydia* is used. Cross-reactivity with different *Chlamydia* species may increase the uncertainty of its value assignment.

Complementary characterization may be performed to confirm the patient origin of the serum by comparing results of fingerprinting of circulating DNA extracted from the serum with that of a paired blood DNA sample [12, 13]. Hemolytic and lipemic indexes are recorded, because of potential interferences in downstream spectroscopic assays. Finally sera must be screened for HIV, HBV and HCV for biosafety purposes.

Fitness-for purpose: The presence of anti-*C. trachomatis* IgG, IgA and/or IgM antibodies in the serum sample can be confirmed with a CE-marked or FDA-approved immunosorbent assay (ELISA). Serum samples with documented standard pre-analytical code (SPREC) and stored at −80 °C are considered fit-for-purpose for downstream application involving serum immunoglobulins. The pre-analytical quality of the serum can be assessed for temperature storage conditions by measuring soluble CD40L (sCD40L) [14], a member of the tumor necrosis factor family of cell surface interaction molecules and an early marker of T-lymphocytes. A threshold of 1.7 ng/mL sCD40L provides 100 % sensitivity in eliminating serum samples which have been exposed to room temperature for over 48 h.

Homogeneity: Serum samples are assessed for homogeneity in terms of microparticle counts (measured with an impedance-based method), and anti-*C. trachomatis* antibodies (measured with an immunosorbent assay).

Stability: Short and long-term stability is measured in terms of anti-*C. trachomatis* IgG, IgA and IgM antibodies, measured by immunofluorescence and/or immunoenzymatic assays.

Documentation of processing procedures: Demographic and anamnestic data from the patient providing the sample are documented, along with the centrifugation conditions used to obtain the serum sample from the blood, including the type of blood collection tube, pre- and post-centrifugation delay and temperature, centrifugation conditions (speed, time, temperature, and brake), storage container, and temperature and freeze-thaw cycles.

3.2 Lung Adenocarcinoma Frozen Tissue-Extracted DNA

As with many cancers with few successful treatment options, there is a pressing need to identify appropriate therapeutic targets and companion diagnostics. The use of comprehensive genomic analysis of lung adenocarcinoma tissue samples is fundamental to this strategy. Comparative genetic analyses of DNA obtained from normal and malignant tumor tissues serve as the support for this, and include whole genome sequencing, characterization of mutation patterns and identification of tumor DNA rearrangements. Potential certification of a lung tumor tissue specimen is described below. Because histopathological classifications are periodically updated by the WHO, the RM producer needs to report the version of the applicable classification.

Purity: The percent of non-necrotic tumor cells in the tumor sample is defined on the basis of a consensus between two certified pathologists. A value of at least 80% of the entire cross-sectional area of the tissue section, excluding the stroma and inflammatory cells, is considered adequate. Sections from both edges of the tumor sample need to be evaluated.

Value assignment and characterization: Historically, tumor characterization (or classification) has been based on histologic and immunohistochemical analyses, with the more recent addition of molecular characterization. Several histologic subtypes are defined for lung carcinomas (adenocarcinomas, squamous cell, small cell, etc.), with further subdivision according to the presence of specific mutations including *EGFR, KRAS, BRAF* and *HER2* and *ALK* translocations. While clinical and anatomical indications of the primary and secondary tumor sites (right or left lung; superior, middle or inferior lobe; segment) contribute to the certification of a tissue sample as a lung adenocarcinoma, the gold standard of diagnosis relies on histopathologic evaluation. Malignant epithelial adenocarcinomas are defined as having "glandular differentiation or mucin production, showing acinar, papillary, or solid with mucin growth patterns or a mixture of these patterns" [15]. Two certified and experienced pathologists must classify the tumor as an adenocarcinoma (WHO 8140/3) and agree on an exact histologic type of adenocarcinoma on the basis of a microscopic examination of a mirror formalin-fixed paraffin-embedded (FFPE) sample, according to the WHO [15] and ICD-O codes. Evaluation of the *EGFR* mutation and *ALK* translocation is now considered mandatory in the diagnostic process, and is determined from FFPE tumor-extracted DNA. Tumor grading is according to conventional criteria, with three grades; well differentiated (grade 1), moderate (grade 2) and poorly differentiated (grade 3). In addition to the histologic characterization, tumors are classified according to the international TNM system for pathologic (pTNM) and clinical (cTNM) staging [16, 17], which provides an indication of the extent of tumor spread on the basis of the primary site (T), lymph nodes (N) and metastases (M). cTNM staging is mainly done with imaging technologies (CT scan and MRI).

Complementary immunohistochemical analyses can be performed on the same FFPE block for the following antigens; CK7 (+), TTF1 (+), napsin A (+), CK5/6 (−), p40 (−), p63 (−), chromogranin A (−), CD56 (−), synaptophysin (−). A minimum panel including napsin and p40 is required to discriminate poorly differentiated adenocarcinoma from poorly differentiated epidermoid carcinoma. *K-ras*, *p53* and *c-erbB2* mutations detected in FFPE tumor-extracted DNA can complement the molecular characterisation. Cytogenetic analysis (the mean chromosome number is near the triploid range [18]) and comparative genome hybridization (CGH) analysis can also complement sample characterization. Deletions on chromosomes 3p, 4q, 5q, 6q, 8p, 9, 13q, and gains on 5p, 8q, 20q are common. Extracted DNA is characterized by quantification with spectrophotometry or spectrofluorometry. Purity (absence of protein contamination) is based on the spectrophotometric ratio A260/A280 (expected to be >1.6) and integrity on agarose gel electrophoresis (expected molecular weight > 20 kb). DNA fingerprinting can be performed with paired adenocarcinoma tissue and blood samples to confirm patient origin [19]. In addition, characterization protocols (DNA extraction methods, elution buffer composition, mutation analyses, thresholds used, etc.) and outcomes are also reported.

Fitness-for purpose: The adequacy of extracted DNA for downstream whole genome amplification (WGA) or CGH studies can be assessed by multiplex PCR [20] or inhibition of amplification by the SPUD assay [21].

Homogeneity: Spectrophotometry is used to assess DNA samples.

Stability: Short and long-term stability studies of DNA relative to specific downstream applications (e.g. WGA, methylation analysis) should be performed with respect to storage temperature.

Documentation of processing procedures: Demographic and anamnestic data from the patient providing the tumor sample, the collection method (e.g. biopsy, surgery, autopsy), sample location, concomitant and prior treatment history are documented, along with details of how the snap-frozen tumor sample was collected, warm and cold ischemia times (time between interrupting the tumor blood supply and tumor excision, and time between tumor excision and snap freezing, respectively), type of storage container and temperature [4, 6].

3.3 Cerebrospinal Fluid from a Patient with Parkinson's Disease

Parkinson's disease is a chronic and progressive neurodegenerative disease of the central nervous system. It mainly affects dopaminergic neurons, and is characterized by both loss of dopaminergic neurons in the substantia nigra, resulting in loss of dopamine in the striatum, as well as loss of the presence of intracellular inclusion bodies in the soma (Lewy bodies) or neurites (Lewy neurites). Diagnosis is based on clinical symptoms, which however are only apparent relatively late in disease evolution, with approximately 80% of the dopaminergic neurons already lost at diagnosis. Efficient tools for early diagnosis before the appearance of motor symptoms (i.e., diagnostic biomarkers) and for defining subtypes will help improve disease management and contribute to decreased disease-associated costs. Various biospecimen types can be used to identify such biomarkers, including cerebrospinal fluid (CSF) and serum, and certification of CSF as a biospecimen source is reviewed.

Purity: Absence of blood contamination in CSF is assessed by determining the presence of hemoglobin or red blood cell counts (RBC). An RBC above 5×10^6/L is considered to render other analytic quantitative measurements uninterpretable.

Value assignment and characterization: Diagnosis of Parkinson's disease (PD) is based on clinical symptoms only (UK Brain Bank criteria) [22] and requires two of the four main symptoms to be present over a period of time, diagnosed by two independent neurologists. These symptoms are bradykinesia (slow and difficult movements), muscular hypertonia (extrapyramidal rigidity of the arms, legs or trunk), tremor, and postural instability (balance difficulties). Dementia is a common late

symptom, reported in around 80% of patients. A myriad of other symptoms are common including olfactory dysfunction, pain, cramps, constipation, pins and needles, orthostatic hypotension, frequent urination, visual dysfunction, sweating, excessive production of saliva, anxiety, REM sleep behaviour disorder, depression, irritability and manias [23].

Value assignment is based on disease stage, and Parkinson subtype (postural instability gait difficulty, tremor dominant or indeterminate). Disease stage is rated using a neurologic scale. The Unified Parkinson's Disease Rating Scale (UPDRS) was developed in the 1980s, however this was replaced by a revised version published by the Movement Disorder Society (MDS-UPDRS) in 2008. This four-part scale includes Part I (non-motor experiences of daily living), Part II (motor experiences of daily living), Part III (motor examination) and Part IV (motor complications). It is a mix of patient, caregiver and clinician evaluations [24].

In patients with a questionable diagnosis, complementary evaluations may be performed to identify more subtle features such as non-specific generalized minor cerebral volume loss by magnetic resonance imaging (MRI) or tomodensitrometry, DaTSCAN to differentiate essential tremor from PD, or olfactory abnormalities with transcranial sonography. Other complementary scales include the Parkinson cognitive status (normal, mild cognitive impairment or dementia), MMSE (Mini Mental State Examination) total score, or the CDR (Clinical Dementia Rating). Neuropsychological tests include a word list test (e.g. CERAD 10-word learning test), a type story recall test, a type visuoconstruction test, a type verbal fluency test, and an attention/executive function test. Finally, patient genotyping may be performed for *SNCA, LRRK2, VPS35, EIF4G1, PARK2, PINK1,* and *DJ-1*.

CSF samples are characterized by protein and glucose concentrations, white cell count, CSF index (CSF IgG to CSF albumin ratio versus the serum IgG to serum albumin ratio) and oligoclonal banding [25, 26]. In the scope of neurodegenerative diseases the key CSF protein biomarkers are α-synuclein, T-tau, P-tau, NF-L, $A\beta_{1-42}$, and DJ-1 [27]. DNA fingerprinting can be performed with paired CSF and blood samples to confirm patient origin [19].

Fit-for purpose: The suitability of CSF for downstream proteomic applications can be assessed by the absence of hemoglobin (ELISA).

Homogeneity: Microparticle counts determined using an impedance-based method can be used to determine CSF homogeneity.

Stability: Short and long-term stability studies of CSF relative to specific downstream applications (e.g. proteomics, metabolomics) should be assessed in terms of temperature.

Documentation of processing procedures: Data to be documented include the lumbar puncture location, needle diameter and type, and syringe and collection tube type, pre- and post-centrifugation delay and temperature, centrifugation conditions (speed, time, temperature, brake), storage container and temperature, and freeze-thaw cycles [28].

3.4 Pancreatic Cancer Cell Line

Tumor cell lines are extensively used to provide early indications as to the efficacy of single and combined drug administration in a clinical setting. They are a useful tool for investigating underlying molecular events which can be exploited to evaluate potential antitumor agents in terms of cell proliferation, viability, and apoptosis and to identify biomarkers for activity and toxicity. Pancreatic adenocarcinoma is an aggressive disease with very poor prognosis due in part to a lack of molecular information on disease development. Here we describe the potential certification of a pancreatic cell line which can be used as a reference material for preclinical analyses.

Purity: Absence of contamination by other cell lines is assessed by short tandem repeat (STR) profiling on eight different STR loci and the amelogenin locus, which can reveal differences of only one or two alleles [12]. Confirmation of the species of origin is performed by isoenzyme analysis or species-specific antibodies [29]. Absence of fungi, yeast and bacterial contamination is confirmed by visual inspection, culturing a sample of the cell medium in nutrient broth or agar, or by PCR (16S, 18SrRNA). Mycoplasma contamination is assessed by Hoechst 33,258 staining and by PCR using validated commercial kits [30]. Viruses are detected by PCR.

Value assignment/characterization: Characterization of pancreatic cell lines includes the clinical history of the donor, *in vitro* and *in vivo* growth characteristics, phenotypic characteristics (adhesion, invasion, migration, tumorigenesis, which can be compared to a well-established and commercially available cell line, such as Capan-1), and genotypic characteristics. Relevant information, documented by two independent certified pathologists includes, but is not limited to, location of the initial tumor specimen, exact histological characterization, pTMN/cTNM classification, and ICD-O classification. Adhesion of the cell line to extracellular matrix proteins (ECM; fibronectin, collagen I, collagen IV, laminin) must be tested, along with percent adherence and time taken to adhere. Invasive ability of the cell line, monitoring cell movement through Matrigel® (a mixture of laminin, type IV collagen, entactin and heparin sulfate) are tested with invasive ability expressed as mean invaded cells per high-powered field, cells/chamber, cells/cm^2 or percent cells completely migrating into the bottom chamber. The length of time allowed for invasion, the cell culture conditions, cell quantification method and invasiveness assay or commercially available kit should be documented.

Levels of pro-angiogenic factors (COX-2, PGE2, VEGF, IL-1α, IL-8) secreted by the cell line is used as a surrogate measure of its angiogenic potential. Pro-angiogenic factors are preferably expressed in absolute units (pg/mL, pg/mg protein, pg/10^6 cells) and the experimental conditions should be documented. Tumorigenicity, the ability of the cell line to produce tumors *in vivo*, is measured in terms of tumor growth following injection of a suspension of pancreatic cancer cells into the subcutaneous tissue of immunocompromised mice. Tumorigenicity is expressed as tumor volume and/or mass (mm^3) formed from a specified number of injected cells (e.g. 10^6 cells) after a specified time (20–50 days).

Complementary evaluations include genotypic mutation analysis of the *KRAS, TP53, CDKN2A* and *SMAD4* genes, which are frequently mutated in pancreatic cancers (http://pathology.jhu.edu/pancreas/geneticsweb/Profiles.htm). It is strongly advised that cell lines be characterized by STR profiling using published STR primers [10] at a recognized central cell bank (ATCC, DSMZ, ECACC, JCRB, RIKEN) and data submitted to a central database (Cell Line Data Base, http://bioinformatics.istge.it/hypercldb/, Cell Line Integrated Molecular Authentication database, http://bioinformatics.istge.it/clima/) [31]. Further analysis can be done to confirm the patient origin of the cell line using DNA fingerprinting on the cell line and the paired whole blood [12, 13, 32], or by immunocytochemistry with tissue-specific markers (e.g. carboxypeptidase B for pancreas specificity) on fixed cells.

Fitness-for purpose: The suitability of a cancer cell line for downstream applications can be assessed by testing its phenotypic characteristics (see above).

Homogeneity: Pancreatic cancer cell lines are heterogeneous populations of cells because of genetic drift and the presence of different tumor cell subtypes and as such, true homogeneity cannot be assessed. Although it may appear inconsistent to certify a reference material without a homogeneity assessment, this reflects the actual clinical situation [33]. Homogeneity can still be assessed relative to attributes such as viable and apoptotic cell subpopulation percentages, or different immunophenotypic cell subpopulation percentages, by flow cytometry.

Stability: Stability of a cancer cell line should be assessed relative to potential genetic drift over sequential passages. STR profile, karyotype (development of aneuploidy and heteroploidy), and gene mutations should be assessed regularly over passages and over long-term cryopreservation.

Documentation of processing procedures: When characterizing a cell line, the original tissue used to derive it, type of collection (biopsy, etc.), warm and cold ischemia times, and transport medium composition are reported. Primary culture conditions should be reported including the method of tissue dissociation (trypsin, collagenase, primary explants culture), composition of culture medium (type of serum, cryoprotectant), cell quantification method, cell culture conditions and extracellular matrix used, batch numbers, passages, seeding details (cell concentration, split ratio, volume per flask), cell concentration and post-thaw cell viability, composition of freezing medium, and freezing protocol. Cell culture aliquots used for the different characterization assays should be traceable to the passage/flask ID.

4 Conclusion

RMs are important for academic or private research groups. They are critical for the IVD and pharmaceutical industry to raise the standards of regulatory submissions involving clinical biospecimen analysis. With few RMs available, obvious exceptions being in the field of microbiology [34], it is clear that the type and number of

certified clinical biospecimens provided by professional biobanks needs to be rapidly and dramatically increased.

The potential for RM certification was demonstrated in this chapter with four examples, including both simple clinical samples (serum, CSF) and clinical sample derivatives (DNA from tissue, cell line from tissue). The materials can be certified for qualitative properties, "*C. trachomatis* acute urogenital infection", "lung adenocarcinoma", "Parkinson's disease" or "pancreatic cancer". Clinical, biological, histopathological, immunological, cell biology and molecular biology data must be collected and reported in order to ensure these qualitative properties are accurate. Although the certified value is qualitative, some of the certification attributes, such as homogeneity and stability, may need to be assessed by quantitative assays.

Biobanks are currently responsible for the collection of data necessary for value assignment, making them ideally placed to develop RM. Compliance to biobank Best Practices [35] is necessary to ensure consistency, robustness and traceability in the chain of biobanking processes, including data collection. Although the level of characterization needed for biobanked samples varies [36], compliance to Best Practice is essential to ensure adequate documentation is available. Accreditation is required for biobanks to operate as RM producers [37, 38]. Therefore, as described in the previous chapter, biobanks can be certified for core biobanking activities, and either be accredited themselves for specific assays, including immunological, molecular biology and histopathology, or collaborate with such accredited laboratories.

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Population Biobanks and the Principle of Reciprocity

Ma'n H. Zawati and Bartha Maria Knoppers

Abstract Samples and data from population studies are stored for long periods of time, and can be accessed by national and international researchers to further their own studies and contribute to their understanding of the impact of a number of factors (e.g., environment, lifestyle) on common diseases and their progression. Part 2 of this Chapter discusses the nature of the researcher's duty to inform, which is the result of an individualistic conception of autonomy. Parts 3 and 4 review this restrictive conception of autonomy, and concludes that it is rooted in a unilateral approach that is incongruous with the nature of biobank genomic research. Finally, Part 5 proposes that autonomy be complemented by the principle of reciprocity, which would not only create a fair and balanced relationship between researchers and participants, but would also recognize the public as a key contributor to genomic research.

Keywords Autonomy • Consent • Duty to inform • Incidental findings • Individual research results • International collaboration • Liberal individualism • Population biobanks • Reciprocity • Trust

1 Introduction

The last two decades have witnessed a key development within the field of biomedicine, namely the transition from genetic to genomic research [1]. Having moved from DNA sequence mapping to the use of haplotypes [2], future advances in our understanding of disease risk and health may well be achieved through the study of

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normal genomic variation across whole populations [3]. Such studies require not only samples and data from multiple sources (e.g., socio-demographic, biological, etc.), but also highly sophisticated infrastructures. Enter population biobanks: longitudinal and largely epidemiological studies designed for a multiplicity of research projects at both national and international levels. In population biobanks, asymptomatic individuals are randomly recruited via health insurance systems or public notice to participate in a "mapping" of heterogeneous populations [3]. After consenting to participate in such a longitudinal study, individuals are asked to provide biological samples and data (derived from self-administered and interviewer-assisted questionnaires, for example). These samples and data are then stored for long periods of time, and can be accessed by national and international researchers to further their own studies and contribute to their understanding of the impact of a number of factors (e.g., environment, lifestyle) on common diseases and their progression [4].

Unlike clinical trials for drugs or devices, future research using population biobanks cannot be specifically identified at the time of consent. This issue has been extensively debated in the literature over the past few years. Authors have debated whether broad consent—a model increasingly used in population studies—satisfies the legal requirements of informed consent [5, 6]. Uneasiness stems from the fact that, in some jurisdictions, a researcher's legal duty to inform is extensive [7]. *Prima facie*, it could be argued that this legal obligation is met by population biobanks. In fact, the epidemiological objectives and longitudinal nature of biobanks can be well described in consent-related documents; this consent can also stipulate the manner in which samples will be conserved, the mechanisms for data security, and, most importantly, the ongoing governance structures for access and ethics monitoring. If a competent adult decides that these conditions and protections are sufficient, why would such consent—broad as to future studies yet also specific as to the governance and oversight of biobanks themselves—be invalid [8]? The answer to this question, it seems, continues to rest on a certain concept of autonomy still applied in both contemporary bioethics [9, 10] and medical law [11, 12]. This concept maintains that the less an individual is expected to benefit therapeutically from a procedure, the higher the duty to inform becomes—hence requiring full and frank disclosure of all facts and probabilities for each research endeavor.

While much ink has been spilled in the last decade on the type of consent required for population biobanks, the following Chapter will not delve too deeply into this debate. Rather, this Chapter focuses on the roots of the predicament created by the researcher's onerous duty to inform. More specifically, this Chapter asserts that such an increase in obligations is the result of an individualistic conception of autonomy (Part 2), which is both restrictive and rooted in a unilateral approach incongruous with the nature of genomic research (Parts 3 and 4). Using population biobanks as a case study, this Chapter will then present a different conception of autonomy, this time founded on the principle of reciprocity (Part 5).

2 Origins of the Conception of Individual Autonomy

Respect for autonomy runs deep in common morality [13]. The word "autonomous" derives from the Greek words "auto" (self) and "nomos" (law), meaning "having one's own laws" [14]. Early use of the word autonomy did not refer to individuals, but to cities that made their own laws [15]. When applied to an individual, the word autonomy can refer to a variety of concepts, including: "the capacity of reason for moral self-determination" [14] and the "liberty to follow one's will; control over one's own affairs; freedom from external influence, personal independence" [14]. Strictly speaking then, autonomy requires two conditions: liberty and agency [13]. Accordingly, someone in a comatose state or in a state of mental incapacity is not considered autonomous.

Philosophers such as Immanuel Kant and John Stuart Mill have strongly influenced current interpretations of respect for autonomy [16]. In his *Foundations of the Metaphysics of Morals* [17], Kant contends that individuals have the capacity to determine their own moral destiny [17, 18]. Based on his view that all persons have unconditional worth, Kant argues that a violation of a person's autonomy is equivalent to treating that person as a means; "that is, in accordance with others' goals without regard to that person's own goals" [13]. Similarly, in his essay "On Liberty" [19], John Stuart Mill focuses on the "individuality" of the autonomous individual. He asserts that nothing should warrant the limitation of an individual's liberty of action, except self-protection [19, 20]. In other words, individuals should be allowed to develop according to their own beliefs.

In brief, autonomy is used broadly and could also be associated with "dignity, integrity, individuality […], responsibility, and self-knowledge" [21]. These diverse conceptions have, unfortunately, resulted in an inability to formulate a unique definition of autonomy. Gerald Dworkin thus notes: "[w]hat is more likely is that there is no single conception of autonomy but that we have one concept and many conceptions of autonomy" [21]. One of these various conceptions is "individual autonomy" [15, 22], which continues to be applied in contemporary bioethics and medical law.

According to Onora O'Neill, individual autonomy "[…] is generally seen as a matter of independence or at least as a capacity for independent decisions and action" [15]. This conception has its roots in Mill's utilitarian principle of liberty. According to Mill:

> That principle is, that the sole end for which mankind are warranted, individually or collectively, in interfering with the liberty of action of any of their number, is self-protection. That the only purpose for which power can be rightfully exercised over any member of a civilized community, against his will, is to prevent harm to others. He cannot rightfully be compelled to do or forbear because it will be better for him to do so, because it will make him happier, because, in the opinion of others, to do so would be wise, or even right. [19]

Mill's focus on individuality stems from his belief that it comprises one of the elements of well-being [19, 23]. Thus, not only should autonomous expression remain unimpeded, but it should also be actively strengthened. Some authors have

labeled this notion as one of liberal individualism [11]. According to Dworkin, it refers more concretely to the:

> […] right of a patient to make his own decisions about important personal matters and to effectuate those decisions (or have them effectuated). Properly understood this would mean that the *patient is entitled to all the information relevant to the decision*, including information the patient does not know he wants or needs. To exercise autonomy the patient would have to be *fully informed* and counseled about what decision to make. [11] (our emphasis)

There are many similarities between the above definition of liberal individualism and the stringent requirements laid out in a number of jurisdictions on the provision of information by researchers to participants. In the United Kingdom for example, disclosure requirements in the context of research are considered greater than those during treatment 'by virtue of the additional contribution to the public interest in particular' [24]—and thus create an even higher duty of 'subjective' disclosure. This is the case for both therapeutic and non-therapeutic research [24]. Similarly, Canadian courts have maintained that participants are entitled to "full and frank disclosure" [25] and that researchers' duties in this regard are as great, if not greater, than the duties owed by physicians in the clinical setting [25]. These legal tenets—often used to create stringent requirements for the provision of information—appear to have liberal individualism at their core. While an emphasis on individual autonomy (with its roots in liberal individualism) may help reduce paternalistic practices [26], it also poses a significant hurdle to genomic research by encouraging a unilateral approach to the researcher-participant relationship. To help us understand this notion of unilateralism, we will briefly review some of the main criticisms of individual autonomy. While most of these were formulated in the clinical setting, reviewing them we will clarify how such criticism could transcend the clinical setting and become significant for researchers that using population biobanks.

One of the main criticisms of individual autonomy is its "highly individualistic" [9] nature. According to some authors, this means that "rights" tend to be claimed "without any sense of reciprocal obligations" [22]. As some authors note, "a competent patient's decision is good simply by virtue of having been made by the patient" [22]. Under individual autonomy, "the patient-doctor relationship is reduced to that of client and technician" [22]. An example of this type of situation is where genetic counsellors are asked to provide non-directive information to patients following a diagnosis [11, 27, 28]. In this context, "non-directive" refers to professionals withholding their opinion so as not to influence their patients [29]. Dworkin finds the roots of this approach in individual autonomy [11]. Other authors have gone so far as to qualify the resulting patient-physician relationship as one of bioethical paternalism, which leads "some doctors to consider mistakenly that unthinking acquiescence to a requested intervention against their clinical judgment is honouring 'patient autonomy' when it is, in fact, [an] abrogation of their duty as doctors" [22].

The above-mentioned examples reflect a sense of unease towards the relationship created by this individualistic conception of autonomy. Indeed, through the resulting unidirectional relationship, the role of the physician is limited to that of a "passive information provider" [30]. Such an approach puts physicians in an awkward position, in which they can no longer easily make their cases by relying

on logical or rational persuasion characterized by the professional use of facts and rationality [31, 32]. Instead, clinical focus is being increasingly placed on perfunctorily providing the patient with the information.

More troublingly, individual autonomy can transcend the clinical setting and have significant implications for what is largely epidemiological, longitudinal research, such as that involving population biobanks. Indeed, population biobanks, like many other genomic research projects, rely on altruistic public participation, as there are no direct, individual benefits. In this case, the application of a unilateral, unidirectional approach is detrimental in that it fails to recognize the public and its involvement (Part 3), or the inherent limitations of this form of research that confront the researcher (Part 4).

3 Individual Autonomy and the Public

Research—especially in population genomics—not only involves contributions from researchers and participants, but also implicates the general public [33]. In fact, while the clinical setting strives to provide direct benefit to the patient, human genetic research in population biobanks aims at benefiting the general public as well as future generations. A sole focus on the autonomy of every individual participant destabilizes the balance created by various stakeholders involved in population studies. Indeed, it would neglect both the contributions made by the public and the fact that future generations remain the ultimate benefactors.

By taking part in a population biobank study, the research participant is largely contributing data and samples for altruistic reasons. Once these data and samples are stored, there is a scientific and ethical imperative for the biobank to make them available to the research community. This increases the statistical power needed to generate useful results, which are then ultimately translated into the clinical environment. The goal is to ensure better health for the population overall, which in turn, increases public trust in these research endeavors. This characteristic of human genomic research has stimulated the emergence of new trends in the field of ethics, among them solidarity and universality [34, 35]. Solidarity refers to a common willingness to share information for the benefit of others, for the common good [8, 34]. Universality, in turn, emphasizes that genetic knowledge is beneficial beyond borders and so for other "publics" [34]. Both trends highlight the importance of public engagement. Indeed, given that genomic research can cover isolated populations or whole countries, it is essential that researchers communicate and consult with policymakers and the public. This engagement could affect decisions relating to the type of consent and access modalities [36]. Indeed, a narrow view of autonomy through liberal individualism devalues public influence over, and underestimates public interest in, population studies and the sustainability thereof. How would a strict access system, which requires that participants explicitly re-consent to every access request to a biobank, efficiently contribute to the orderly translation of knowledge to the clinic? How would such a narrow approach increase public trust in these research endeavors?

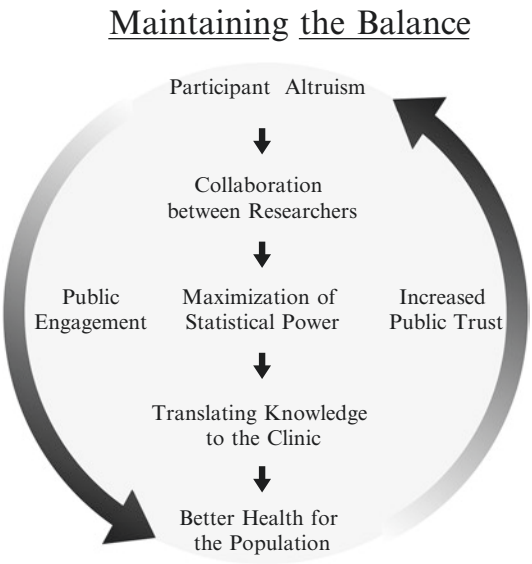

Fig. 1 Maintaining the balance. This figure portrays the delicate balance population biobanks have to maintain in order to sustain the public's trust in their endeavors

The reality is that the public plays a central role in population research, and that this role is fuelled by trust, a shared belief in the common good, and thoughtful engagement. These necessities are not captured by individual autonomy because the latter has become shorthand for independence [37] (in this case, participant independence). This creates a negative imbalance that will ultimately affect all the different stakeholders involved (Fig. 1).

4 Individual Autonomy Does not Consider the Limitations of all the Parties Involved

Autonomy and its unidirectional focus on research participants solely as individuals also creates a general inability to consider the limitations of both parties in the researcher-participant relationship. A good example of this inability is the disclosure of information surrounding future access to data and samples. Here, the unilateral approach focuses only on what needs to be provided to the participant—in this case, everything—without fair consideration of the possible confines in which researchers might find themselves. Population biobanks are clearly limited in what information they are able to divulge. Moreover, as mentioned above, it would be too cumbersome for these projects—which usually involve more than 10,000 participants—to obtain individual re-consent every time a request for access is received [38].

Mill's liberal individualism calls for society to allow individuals to progress according to their own views, as long as they do not interfere with the autonomous expression of others or "unjustifiably harm them" [13]. That said, Mill made no

mention of the possible limitations that could arise from the strengthening of autonomous expression. The nature of consent and the specificity of its content are just two examples of such limitations in a field where increasingly cutting-edge technologies are being used to generate vast amount of non-interpretable data.

The return of individual research results (IRRs) and incidental findings (IFs) is another case in point. It is also one that illustrates the limitations faced by both researchers and participants in genomics and population biobanks. While IRRs pertain to the objectives of a research project, IFs fall outside the scope of the project [39]. By definition—and if we follow the principle of liberal individualism—both types of findings could fall under a broad duty of disclosure, which is limited in the context of genomics. Indeed, the nature of the information discovered (whether IRRs or IFs) will not necessarily provide the participant with an actionable result. It may even lack analytical validity or any form of clinical significance [7]. The imposition of a stringent duty to return such findings not only creates more harm than benefit, but could also put the researcher in a difficult and unduly onerous position. Indeed, researchers might not always have the required in-house expertise to feed this information back to the participant. Even if they have the requisite expertise, researchers should nevertheless take into consideration the participants' situations and constraints (e.g. social, familial, etc.). Disclosure of information and of results in research should be personalized, and should not follow a "one-size-fits-all" approach. Moreover, "return" in population biobanks could be considered to create a therapeutic misconception between research and the clinic, or be considered an inducement [40]. Population biobanks could be overwhelmed with obligations that are essentially inimical to genomic research (in general) and population biobanks (in particular). This has the damaging effect of breaking the fabric of trust between all parties involved in population studies (Fig. 2).

Participants trust biobank researchers with their data and samples and expect that any benefits accrued will be achieved through collaborative, high-quality research. The public trusts that any funding of these endeavors will generate benefits for future generations [41]. In turn, the biobank researcher trusts that the research community will use these data and samples according to the agreed-upon terms and

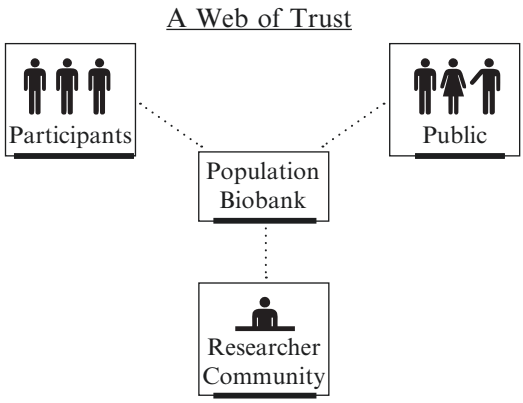

Fig. 2 A Web of Trust. This figure identifies the main stakeholders in the population biobanking sphere. It aims to exemplify the importance of moving away from a bilateral participant-researcher relationship to a multilateral one that also includes the public as well

conditions, and will strive to return derived data back to the biobank to enrich its resources [42]. Through an individualistic conception of autonomy, researchers do not enter into relationships of trust with participants, but rather are forced into unremitting professional accountability [15]. This unidirectional relationship weakens the remaining threads in the joint web of trust.

5 The Case for Reciprocity

Presented by some authors as an emerging trend in bioethics [34, 43], and widely used in public health ethics [44], reciprocity is based on the premise that individuals "incur obligations to help or benefit others at least in part because [they] have received, will receive, or stand to receive beneficial assistance from them" [13]. More concretely, reciprocity is associated with mutuality, which requires that "parties [be] jointly bound as regards the benefits and risks from their interaction and that one's obligation of return is conditional to the value of the benefit received" [45]. This, in turn, requires both trust and empowerment [45]. Trust is strengthened by "positive collaboration and experience between […] parties" [45]. Empowerment refers to the idea that "participants are protected in mobilizing themselves efficiently and that their contribution to the research enterprise is acknowledged and respected" [45]. In other words, reciprocity is based on a participatory approach that: "[…] demands proportionate balancing of the benefits and burdens of social cooperation […] so that any resulting inequalities in benefits and burdens resulting from some relevant social practice are not unfair or intolerable" [44].

Though disclosure is an important component of reciprocity, clarity and transparency as to proper governance in return for trust are its driving force [46]. That said, is the principle of reciprocity better-suited to large-scale population studies? More importantly, does it represent a multilateral approach that could complement the principle of autonomy in researchers' duty to inform? The answer to both questions is yes. Autonomy supplemented by reciprocity would be grounded in fairly balanced, communal obligations. This would help to alleviate the deficiencies of an individualistic conception of autonomy as presented in previous sections (Parts 3 and 4).

First, reciprocity would be grounded in fair and balanced obligations because it follows the general principle that individuals who "make a social contribution through accepting burdens of research risk should receive benefits in return, but not by disproportionately increasing burdens on others" [47]. For example, the consent process would consider that researchers are necessarily and honestly limited in the amount of information that they can provide to participants on future use of samples and data. The same applies for the return of IRRs and IFs: researchers should not be under ambiguous, onerous or speculative obligations to return findings in the context of biobanks. As some authors have noted, reciprocity is "fundamental to the very concept of justice" [48]. In other words, "*when you can*, return good in proportion to the good you receive" [48] (emphasis added). Reciprocity increases the level of trust between participants and researchers by eliminating inefficient and onerous obligations for researchers (whether for consent or for individual research results).

Second, reciprocity is communal because it establishes an "ongoing and long-term relationship between participants, researchers and society" [49], and values prior consultation and communication with the general public [34]. In other words, reciprocity recognizes the public as a distinct party whose opinions and thoughts could shape policies and the overall direction of a research project. As seen in Fig. 1, such engagement increases public trust, which, in turn, sustains the continued altruistic participation of individuals who are generally asymptomatic. Reciprocity also facilitates the overarching goal of population biobanks by creating generalizable knowledge for the benefit of future generations and by regularly communicating to the population the results of research gleaned by accessing the biobank. But, by excluding onerous obligations that unduly limit access to data and samples through delays and constant re-consent, reciprocity facilitates collaboration between researchers and so maximizes statistical power, which translates into better science for population health. Successfully achieving this not only impacts the population, but also recognizes participant contributions, which lie at the core of the notion of empowerment. What better way to nurture and sustain the tri-partite, trust-based relationship between the researcher, the public and the participant than to apply reciprocity to the researcher's duty to inform?

6 Conclusion

The move towards personalized medicine will require the creation of reference maps of whole populations. These maps will serve "as controls for replication, comparison, and validation of personalized genomic discoveries and profiles" [3]. Population biobanks are at the center of important undertakings such as public health planning; the only way to achieve these goals is to collect, store and share data and samples for future unspecified research. Today, at the international level, the focus is on facilitating such collaborative efforts. In that respect, the Public Population Project in Genomics and Society (P^3G)—an international consortium whose members are leading public organizations involved in large-scale genetic epidemiological studies—is developing research tools for effective collaboration between researchers, whether in ethics, information technology or data harmonization [50]. In the same vein, the Global Alliance for Genomics and Health (GA4GH) is building an endeavor that fosters "frameworks and tools for genomic and clinical data sharing […] [as well as] the translation of the benefits of research for health" [51] while recognizing the contribution of the scientists that make this possible.

While this text is in no way a repudiation of the concept of autonomy, it represents a call for a complementary principle that could offer a more proportionate approach to the researcher's duty to inform.[1] Proportionality here refers to the imposition of a fair and balanced intensity of professional responsibilities by taking into

[1] "Critiques of autonomy should not be taken as suggestions to do away with it. Instead, we should seek principles to complement it, especially when autonomy falters or is inapplicable" [52].

account the types of services they are providing, the multilateral characteristics of their duties, and the nature of the research. Additionally, it is also a call for a principle that acknowledges the important role played by the public, premised on multilateral trust and transparency. Researchers need it and participants deserve it.

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Biobank and Expertise Networks

R.E. Hewitt, W.E. Grizzle, P.H. Watson, Y. Lee, J.-H. di Donato, and J. Vaught

Abstract Since the year 2000 the number and size of biobank networks has grown in response to the rising research demand for high quality, well-annotated biological samples. So too have the number of expertise networks in which individuals share knowledge, to advance the field of biobanking. This chapter reviews the characteristics of biobank networks and provides case studies of three well-established examples: the Cooperative Human Tissue Network in the USA, the Canadian Tissue Repository Network (CTRNet) and the Korean National Network for Research Resource Centres (KNRRC). Next, there are case studies of three successful expertise networks: the International Society for Biological and Environmental Repositories (ISBER), the European, Middle Eastern and African Society for Biopreservation and Biobanking (ESBB) and the French Club 3C-R. This is followed by comparison of biobank and expertise networks, where it is noted that as biobank networks expand to the national and international level, they take on many of the characteristics of expertise networks. The chapter concludes with some

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thoughts about the shared objectives of biobank and expertise networks and the need for good communication between networks.

Keywords Biobank network • Expertise network • Collaboration • Communication • International • Standards • Education

1 Introduction

Important milestones in the development of molecular biotechnology include development of DNA sequencing techniques in 1974, invention of the polymerase chain reaction in 1980, launch of the human genome project in 1990, and announcement of the first draft of the human genome sequence in 2000. In this period, high-throughput methods of analysis have been developed across the spectrum of important biomolecules and as a result the research demand for biological samples has increased dramatically. It has been increasingly difficult for single biobanks acting alone to cope with this demand for samples, which is one of the main factors that has encouraged biobanks to join forces and to form cooperative networks on a regional, national and even international scale. The functioning of networked organizations has been greatly assisted by telecommunications networks, allowing telephone, email and other forms of communication. Since the mid 1990s, the Internet has had an enormous impact on culture and commerce, allowing rapid and effective communication by email, and making possible the World Wide Web with its websites, online discussion forums and social networking. Against this background of technological developments, it is not surprising to see that the number of major national and international biobank networks has increased markedly in the past 20 years (Fig. 1).

This chapter will start with a brief history of biobank network development, followed by a description of general features of biobank networks, and three case studies of major biobank networks. Next, expertise networks will be described, with three further case studies. The chapter will end with some conclusions on how all the different network types can and do work together and synergize.

2 Definitions

It is generally agreed that biobanks manage collections of biological specimens with associated data, maintained for a wide range of scientific and biotechnology purposes [1, 2]. Such Biobanks are sometimes described by other names like biorepositories, Biological Resource Centres (BRC) and Research Resource Centres (RRC). Increasingly, over the past 20 years, such biobanks have formed collaborative groups or networks. For the purpose of this article, the term “Biobank Network”

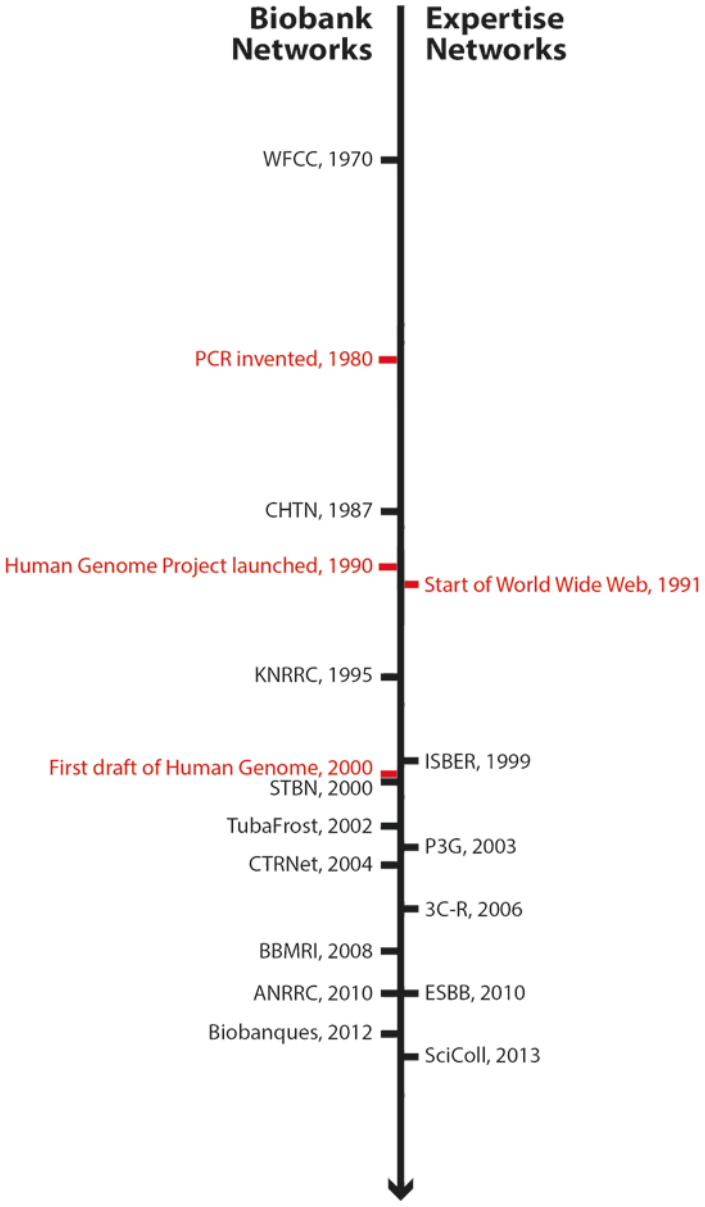

Fig. 1 Timeline showing the years in which different biobank networks and expertise networks were founded in relation to key milestones in molecular and information technology

will be used to describe groups of biobanks that work together in a coordinated manner for the benefit of research users, and usually to provide a unified service. In addition, the term "Expertise Network" will be used here to describe groups of people, organized as societies, associations or clubs, who share a common interest in biobanking and who work together to advance the biobanking field.

3 Biobank Networks

3.1 Historical Development

The World Federation of Culture Collections (WFCC) founded in 1970 [3] was one of the first biobank networks. It is concerned with the collection, authentication, maintenance and distribution of cultures of microorganisms and cultured cells. It pioneered the development of an international database on culture resources worldwide and the result is the WFCC World Data Center for Microorganisms (WDCM), now maintained at National Institute of Genetics (NIG), Japan.

One of the first biobank networks of human tissue was the US Cooperative Human Tissue Network (CHTN) founded in 1987. This was funded by the US National Cancer Institute to provide researchers with human tumour tissue [4]. This well established biobank network, with its 28-year track record, is described in detail later in this chapter. Another example to be explored here in detail is the Canadian Tumour Repository Network (CTRNet) founded in 2004 [5]. This tumour banking network which spans English and French-speaking regions of Canada, has been actively involved in advancing the biobanking field and provides a number of innovative solutions for biobank management. A further well established example that will be considered in detail is the Korean Network for Research Resource Centres (KNRRC) founded in 1995 [6]. This unique and diverse network includes biobanks of human, animal, plant and microbial samples, and has central services to support education, training, and certification of member biobanks. The KNRRC is itself a part of a wider Asian biobank network, the Asian Network for Research Resource Centres (ANRRC).

The pan-European Biobanking and Biomolecular Resources Research Infrastructure (BBMRI) is described in a separate chapter of this book, and so will not be described further here. This project which officially commenced in 2008 is unique in its size and complexity, and is in the process of forming a network of networks across the culturally-diverse member states of Europe [7]. Prior to the broader BBMRI initiative, a large number of biobank networks had been established in Europe and several of these have published valuable accounts of their experience. These include the Spanish National Tumour Bank Network founded in 2000 [8] and the TubaFrost virtual tumour bank network founded in 2002 [9–14]. Another example is the Telethon Network of Genetic Biobanks

Table 1 Selection of biobank networks and expertise networks

Name of network	Scope[a]	Type	Region	Language	Founded
Asian Network for Research Resource Centers (ANRRC)	H, A, P, M	Biobank	Asia	English	2009
Australian Breast Cancer Tissue Bank (ABCTB)	H-T	Biobank	Australia	English	2004
Biobanking and Biomolecular Resources Research Infrastructure (BBMRI)	H	Biobank	Europe	English	2008
Biobanques	H, M	Biobank	France	French	2012
Canadian Tumour Repository Network (CTRNet)	H-T	Biobank	Canada	English	2004
Confederation of Cancer Biobanks (CCB)	H-T	Biobank	UK	English	2006
Cooperative Human Tissue Network (CHTN)	H-T	Biobank	USA	English	1987
EuroBioBank	H	Biobank	Europe	English	2001
Frozen Ark Consortium	A	Biobank	Global	English	2007
Italian Network of Oncological Biobanks (RIBBO)	H-T	Biobank	Italy	Italian	2004
Korean Network for Research Resource Centers (KNRRC)	H, A, P, M	Biobank	S. Korea	Korean	1995
Microbial Resource Research Infrastructure (MIRRI)	M	Biobank	Europe	English	2012
North German Colon Cancer Network (ColoNet)	H-T	Biobank	N. Germany	German	?
Shanghai Biobank Network (SBN)	H	Biobank	China	Mandarin	2010
Spanish National Tumour Bank Network (SNTBN)	H-T	Biobank	Spain	Spanish	2000
Telethon Network of Genetic Biobanks (TNGB)	H-RD	Biobank	Italy	Italian	2008
TubaFrost	H-T	Biobank	Europe	English	2002
Tumorotheques du Cancéropole PACA	H-T	Biobank	France	French	?
World Federation of Culture Collections (WFCC)	M	Biobank	Global	English	1970
3C-R	H, A, P, M	Expertise	France	French	2006
Biospecimen Research Network (BRN)	H-T	Expertise	USA	English	2006
European, Middle Eastern and African Society for Biopreservation and Biobanking (ESBB)	H, A, P, M	Expertise	EMEA	English	2010

(continued)

Table 1 (continued)

Name of network	Scope[a]	Type	Region	Language	Founded
Global Genome Biodiversity Network (GGBN)	H, A, P, M	Expertise	Global	English	2013
International Bar Code of Life (i/CBOL)	H, A, P, M	Expertise	Global	English	2010
International Society for Biological and Environmental Repositories (ISBER)	H, A, P, M	Expertise	Global	English	1999
Marble Arch Working Group (MAWG)	H	Expertise	Global	English	2005
Society for Preservation of Natural History Collections (SPNHC)	H, A, P, M	Expertise	Global	English	1985
Public Population Project in Genomics and Society (P3G)	H	Expertise	Global	English	2003
Scientific Collections International (SciColl)	H, A, P, M	Expertise	Global	English	2013
Society for Low Temperature Biology (STLB)	H, A, P, M	Expertise	Global	English	1964
Society for Cryobiology	H, A, P, M	Expertise	Global	English	1964

[a]*H* human, *H-T* human tumor, *H-RD* human rare disease, *A* animal, *P* plant, *M* microbe

created in 2008 [15], which itself is part of the EuroBioBank network of rare disease biobanks founded in 2001 (Mora et al. 2015).

A few additional examples of biobank networks are shown in Table 1 and this represents only a small sample of all the existing biobank networks: the BBMRI catalogue of biobanks lists a total of 43 biobank networks in Europe alone: https://www.bbmriportal.eu/bbmri2.0/jsp/core/menu.jsf.

3.2 Advantages of Biobank Networks

There are two major reasons for the growth of biobank networks in recent years. The first is that as mentioned earlier, single biobanks have been unable to meet the increasing research need resulting from the development of high throughput molecular technologies. The second is the single biobanks have been unable to meet the demands of research studies on rare diseases, or rare sub-types of more common diseases. To satisfy these demands, it has been necessary for groups of biobanks to collaborate in sharing collections. So that research on pooled samples originating from different biobanks can be effective and meaningful comparisons can be made, it is essential that the networked biobanks standardize their policies and procedures. The formation and management of a biobank network therefore requires very careful organization and coordination.

The ability of networked biobanks to pool their expertise provides many benefits: firstly, there is the economic benefit that senior managers and specialist staff can be shared by multiple biobanks, resulting in reduced manpower costs; and secondly, the shared expertise makes it easier to find the best solutions for all in specific areas like informatics, quality management, policy development and public relations. Another advantage of biobank networks is that, compared with single biobanks, it is easier for them to justify value-added services like DNA extraction, tissue micro-dissection and tissue microarrays [16]. So in summary, biobank networks allow for enhanced access to samples, they have the potential to provide a higher quality, more comprehensive service and to allow for economies of scale that lead to greater financial efficiency. In addition, they can respond jointly to calls for grant funding. Biobank networks are therefore better able to meet the needs of all the stakeholders, including patients, the general public, sample providers, researchers, and funding agencies. With all these benefits, biobank networks have the potential to be more sustainable than stand-alone biobanks [17].

3.3 Design and Management

The design of biobank networks is highly variable. For some the network is simply a group of biobanks with a single coordination centre, whereas others are a network of networks, that may extend to regional, national or international levels (Fig. 2). Within these networks there may be many different patterns of operation depending on local circumstances.

A classification of biobank networks has been provided by Shickle and co-workers, based on a systematic survey of 33 biobanks in nine countries [18]. They identified the following types of biobank network:

1. Storage networks, in which multiple biobanks or collectors share a single storage facility to reduce costs.

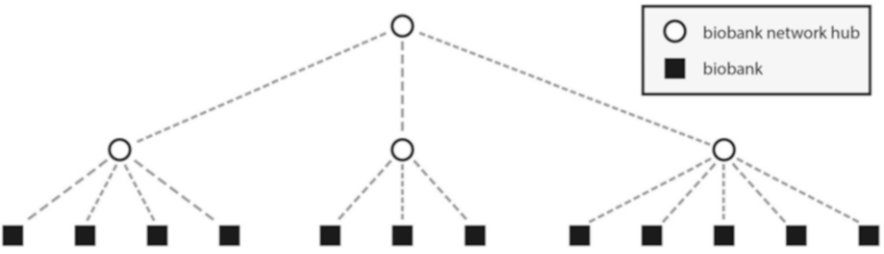

Fig. 2 Illustration of a biobank network. In this example, there are three simple biobank networks, where biobanks are linked directly to a hub. Then three hubs are linked to a single hub (which could represent a national hub), forming a network of networks

2. Bring-and-share storage networks, which are similar to storage networks, except that lower storage fees are offered to collectors willing to allow outside access to their samples.
3. Catalogue networks, in which multiple biobanks put sample data on a single database that is searchable by external researchers seeking samples for their research.
4. Partnership networks, which are groups of biobanks connected by a formal contract or partnership agreement, and where there is sharing of costs and samples are considered to "belong" to the partnership.
5. Contribution networks, in which the biobank is not responsible for collection of samples, and only stores and distributes tissues.

Shickle and coworkers noted that many networks were a mixture of these types, rather than purely one type or another. They also identified a sixth category of network which they call "expertise networks", which are networks of people who share biobanking knowledge rather than samples [18]. These networks are highly relevant, but do not meet the definition of biobank network used in the present chapter.

No matter what the design, all biobank networks require some coordination. In order to function effectively, this often takes the form of an office with a network coordinator in charge. The coordination office may be involved in managing the day-to-day operations of the network, communication and ensuring that all the main activities are standardized and coordinated. It is often responsible for definition, development and implementation of standard operating procedures (SOPs) and standard policies across the network. SOPs need to cover many different areas including administration, participant management, records management, facilities management, quality assurance, safety, training, materials handling and materials release. Standard policies are required for informed consent, privacy and security, health and safety, records and documentation, material release, and governance. It may also be responsible for the design and implementation of a common informatics platform, for database management and for the selection of a minimal data set, and controlled terminologies. The coordination office must also manage tissue requests, interact with institutional review boards (ethics committees) and scientific review and tissue allocation committees and communicate effectively with researchers. It may also take responsibility for an overall quality management system that usually takes the form of a certification or accreditation process for the network as a whole. In addition, the coordination office could take responsibility for managing centralized laboratory services to provide tissue microarrays or molecular extracts for example. It may also take responsibility for producing reports, catalogues and web portals, budgets, grant applications, and publications [15, 19, 20].

Despite the many advantages of biobank networks, their success depends on the support and cooperation of a number of different stakeholders. The networking of pre-existing stand-alone biobanks can present particular problems, if this is a top-down initiative and is not handled sensitively. This issue was once prevalent but is now dissipating and has some of its origins in the diverse funding and origins of many older biobanks and the competitive culture in research. The managers of a

stand-alone biobank may need to be convinced of the benefits of declaring or sending all the samples they collect to a centralized storage facility, if this results in loss of control of their collection. In some circumstances, it may be enough to provide financial support, additional shared staff, access to additional samples for research, or some other benefit to the supplying biobank or institution. Sometimes, hesitation can be alleviated if only a portion of samples from each case are required by the central storage facility. Other times, the best solution may be to adopt a different network design, like the catalogue network model where samples are stored at the collection site but sample data is transferred to single network database that is searchable by each member of the network and even by external researchers. This custodianship problem appears to be universal, and for the TubaFrost project that was developed in an era when this was a significant issue "one of the most important underlying principles within the network is that the local collector retains complete custodianship over the collected tissue. The samples are not given to a large organization, which takes top-down decisions on participation of requests of tissue samples, but instead the tissue samples remain easy to access by the collector for use within their own organization, yet still available to the larger network" [11].

Another management issue addressed by the TubaFrost project relates to international biobank networks and the problems that arise in the case of samples collected in one jurisdiction and used in another. To answer the question of which country's regulations should be applied, TubaFrost chose to create a coordinating rule: "if tissue may legitimately be used for a certain kind of research in the country where it was taken and under whose jurisdiction the patient falls, it may also be used for such research in the country where it is sent to in the context of a scientific program even if in that other country other regulations would apply for research with residual tissue taken from patients under their jurisdiction" [14].

As well organized and professional infrastructures, modern biobanks have the opportunity to participate in a number of different biobank networks. This brings the additional challenge, that belonging to more than one biobank network makes it necessary to comply with many different sets of requirements for SOPs, database specifications, objectives, and performance indicators. To meet this challenge, biobanks must find the right balance between their own quality management requirements and requirements of the different biobank networks to which they belong.

3.4 Example 1: The Cooperative Human Tissue Network

The Cooperative Human Tissue Network (CHTN) was developed with a view that a cost effective tissue resource could be developed to aid investigators throughout the United States of America (USA) in obtaining tissues needed to support their research. The CHTN was established in 1987 as a cooperative group of three institutions whose goal was to supply investigators with high quality human tissues in order to increase research in cancer. The CHTN is now composed of six institutions: Nationwide Children's Hospital, The Ohio State University Hospital, The University

of Alabama at Birmingham, The University of Pennsylvania, The University of Virginia, and Vanderbilt University; the CHTN supplies human tissues to investigators throughout North America and occasionally internationally [21, 22].

The CHTN operates regionally with each member institution responsible for providing tissues to investigators within a different geographic region of North America. For example, The University of Alabama at Birmingham is responsible for the investigators located from Texas to Virginia and from Kentucky southward. Also, it covers providing tissues to investigators in Puerto Rico. Investigators apply for tissues from the CHTN Division responsible for their geographic region and complete a detailed application and agreement [21]. A wide range of de-identified tissues are provided including solid tissues and bodily fluids. These include malignant, pre-invasive neoplasia, benign, non-neoplastic, diseased and other specimens such as matched uninvolved. Specimen preparations include fresh (non-frozen), frozen, fixed, paraffin embedded/blocks, frozen sections or paraffin embedded slides, tissue microarrays, RNA/DNA, nitrocellulose and other blots, and special investigator requested preparations.

When an institution cannot fulfill an investigator's request, the request is networked to the other divisions of the CHTN. Networking is facilitated by a common CHTN informatics system. All operations of the CHTN are governed by a detailed Operations and Procedure Manual and the quality of tissues is emphasized by a quality control examination that is performed on mirror images of the individual specimens provided to investigators. The de-identified specimens are accompanied by surgical pathology reports that are blinded as to the identities of the patient, site, and pathologist. Because this basic model of biorepository operations has been very successful, it has remained essentially unchanged for the over 25 years of the CHTN's operation.

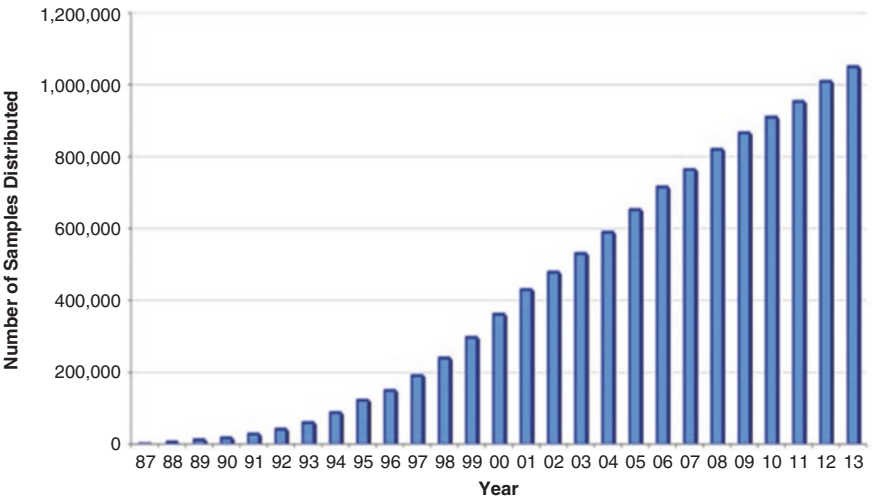

Fig. 3 Total CHTN samples distributed (1987–2013)

The CHTN has proved to be a very successful biorepository, distributing over one million tissue aliquots to over 3300 investigators since it was founded (Fig. 3). To date, the services provided by the CHTN have supported over 3700 publications with over 31% of these publications appearing in journals with a 5-year impact factor > 5 (Journal Citation Reports®, Thomson Reuters).

The success of the CHTN has been primarily due to the prospective biorepository model under which it operates. In this model, investigators specify what tissues they want collected and how these tissues are to be processed (e.g., fresh, finely minced in media). A coordinator acts as a central contact and aids in fulfilling common administrative functions. The CHTN's indices of success are the number of specimen aliquots provided to researchers. There is no credit for collecting or banking tissue specimens which are not utilized. This complete focus on distributing specimens to investigators has been important to meeting the goals of the CHTN.

The CHTN and its member sites such as the Southern Division of the CHTN at the University of Alabama (UAB), serve as a network of expertise for the biorepository community. Some CHTN members have contributed to ISBER as founders and officers and to each version of ISBER Best Practices as authors (e.g., Dr. Grizzle and Ms. Sexton) and as editors (e.g., Ms. Sexton). The CHTN sites also synthesize the literature as to biorepository operations and sciences and provide this information together with their expertise to the investigators to whom specimens are requested as well as to national and international biorepositories, institutions and governments to which consultations are provided by CHTN members. Thus, the divisions of the CHTN see their mission as more than a source of biospecimens, but also as leaders in developing, expanding and improving international biorepository operations.

3.5 Example 2: Canadian Tissue (Formally 'Tumour') Repository Network

Background: In Canada, rising demand from the cancer research community led to the creation of several tumour banks funded by national and provincial grant funding mechanisms in the decade spanning 1993–2003. This spurred development of some of the key elements of modern biobanking activity and the future requirements for more advanced research biobanks became clear. By 2003 knowledge had accumulated around the process of biobanking and a clear need had emerged to capitalize on these tumour bank models to advance biobanking capacity. However, it was also clear that local divergences in practices and standards and quality had emerged, as these banks had been developed through mostly individual research investigator driven programs [23, 24]. While not important in the short term, it was recognized that these divergences

would limit Canadian research in the long term when biospecimens from multiple sources would be needed for example for the large "omic" scale projects that were just appearing on the research stage at that time. Therefore, the Institute of Cancer Research (ICR) at the Canadian Institutes for Health Research (ICR-CIHR), decided that the next step in the evolution of tumour banking in Canada should be to fund a network that would leverage this previous investment and focus on developing common standards, coordinating steps to harmonize existing banks, and improved research access to standardized biospecimens. A very important and visionary aspect at the time to the terms of reference for funding of this network was to stipulate that no funds could be used for the actual process of collection of biospecimens or annotating data. This effectively forced the early participants in the network to focus on components that form the 'glue' between biobanks and that would make it an effective network for users.

Network composition and focus: The Canadian Tissue (previously 'Tumour') Repository Network (CTRNet), is now a consortium of leading Canadian biorepositories that aims to support health research by enhancing biobanking capacity and improving product quality through standardization. The six charter biobanks comprised regional tumour focused biorepositories, provincial programs, pan-provincial networks and one national network that had each been established at different times from 1993 to 2004 through institutional, provincial, or national funding mechanisms. These diverse origins had served to create original, competitive, and divergent designs for biobanking each responsive to different governance and stimuli relevant to the research strengths of their hosts and funders. The major focus for CTRNet in its first phase from 2004 was therefore to share experience, identify the differences that might be a barrier to pan-Canadian research, and to develop solutions and a shared catalogue to enhance research access. In its second phase since 2010, CTRNet has developed mechanisms to communicate these solutions across the large arena of cancer research and more recently also other realms of health research (hence the recent change from 'Tumour' to Tissue' in the network name). At the core of its many platforms developed to support biobanking is a national Registration-Certification Program that was designed to be applicable to the entire spectrum of research biorepositories within Canada [25]. As this program gains acceptance CTRNet is expanding its membership and research access to biospecimens through a national register of biobanks linked to the existing national biospecimen catalogue. Those biobanks that proceed to the certification phase are also laying a new foundation for research access to standardized biospecimens conforming to the national standards of CTRNet. Other platforms linked to this core are an open access biospecimen inventory solution (ATIM), a centralized biospecimen QA platform [26], education and training programs. These are now made available to the nationally beyond the cancer research community and internationally through the CTRNet Biobank Resource Center.

3.6 Example 3: Korean Network for Research Resource Centers

In Korea, along with the fast economic growth, the scientific and technological fields advanced rapidly in 80s and 90s. It was recognized that there are research labs that have accumulated specimens, derivatives and research products valuable to other scientists. These resources require expertise for collection and preservation and are in need of support for management to meet the public needs. The 'Korea National Research Resource Center (KNRRC)' project was launched as a part of special plan on building infrastructure for supporting basic science in 1995. At first, five labs were started as Special Research Resource Centers (RRCs) with the goal of providing reliable resources for scientific researches and applications. By 2005, the number of RRCs increased to 30 and one core center for microbial resources started. For total management of RRCs, the KNRRC headquarters (HQ) was established in 2008. In the same year, Korean government set the 'National Master Plan for Management and Utilization of Biomaterials for the efficient and long-term support on scientific research.

Currently, there are five core centers and 36 RRCs: 11 microorganism (Fungal Genetic Resources, Metagenome Resource, Bacteriophage, Pathogenic Viruses, Plant Virus, Korean Lichen & Allied Bioresources, Oral Microbiology, Marine Microalgae, Antimicrobial Resistant Microbes, Helicobacter Pylori, Environmental Microorganisms); six human-origin (Liver Cancer, Prostate, Leukemia, Gynecologic Cancer, Korean Cell Line Bank, Human Serum Bank); seven animal (Parasite Resource, Aging Tissue, Neuromarker Resource, Animal Bioresources, Bovine Genome Resources, Arthropods of Medical Importance Resource, Zebrafish; four plants (Bioactive Natural Material, Medicinal Plant Resources, Ginseng, Plant DNA; eight fusion-matter (Polymer Pro-drug Precursor, Porous Nanoparticle, Crystal, Modified Nucleic Acid Systems, Noncentrosymmetric Materials, Color Tunable Microparticles, Sphingolipid, Phosphor Resource) RRCs [27].

RRCs are performing collection, characterization, distribution, deposition, and services as recommended by OECD (Biological Resource Centers, 2001). The main goals of core centers are to ensure quality of resources in RRCs and to support new and discontinued RRCs. The HQ and core centers are evaluated in every 3 years while RRCs are supported for 5 years and can be renewed.

The KNRRC HQ established an integrated management system that consists of inventory management system (KNRRC Inventory Management System, KIMS), headquarters' homepage, RRCs' homepage, outcome management system (KNRRC Outcome Management System, KOMS) and DB for all resources. The HQ has published 14 volumes of 'KNRRC Best Practice Guidelines for RRCs', since. The first volume, the general operation management was developed into a Standards of Private Sectors (de-jure standard) for KNRRC facilities and approved by Korean Standards Association (KSA). This standard (SPS-KNRRC 0001-2008:2013) comprises the basic requirements and criteria of KNRRC operation and management and gives general provision of a quality management system. Other missions of HQ

are providing educational programs to train RRC staffs, workshops and overseas training programs to improve quality of resource management as well as to promote collaborative researches among Asian resource centers.

In 2013, KNRRC collected more than 100,000 new resources and distributed 60,399 resources to universities, research institutes and industry. Also, KNRRC provided 123 technical services and signed 13 memorandum of understanding (MOU) with ten domestic institutes and three international institutes for cooperation. Using the distributed KNRRC resources, 678 SCI papers were published and 20 patents were applied or registered.

KNRRC played a central role in organizing Asian Network of Research Resource Centers (ANRRC) along with RIKEN-BRC of Japan and IMCAS of China in 2009. The three institutes have been hosting annual meetings in turn. Several committees are working on information management, biobanking of human-derived specimens, biodiversity and regulations, and international affairs. Currently, ANRRC has 192 registered members from 96 institutes from 14 countries [28]. Most ANRRC members are non-profit bioresources centers, biobanks, biorepositories and culture collections dealing with microorganism, animal, plant, and human-derived specimens supported by the national government and/or equivalent funding agencies. The main interests are establishment of biobanks, quality management of resources and information, development of common guidelines and preservation of bioresources. The Nagoya Protocol on Access to Genetic Resources and the Fair and Equitable Sharing of Benefits Arising from their Utilization, a supplementary agreement to the Convention on Biological Diversity has entered into force on 12 October 2014. This may add further burden to BRCs and require coordinated efforts to harness the public benefit.

The ANRRC submitted a petition regarding Nagoya protocol and its possible detrimental effect on exchange of bioresources for non-commercial scientific research. The ANRRC members plan to expand cross-training programs of researchers and to promote collaborative research on bioresources. ANRRC have established an affiliate relation with ISBER (International Society for Biological and Environmental Repositories) and also with ESBB (European, Middle-Eastern and African Society for Biopreservation and Biobanking).

4 Expertise Networks

During the same time period that many biobank networks came into existence, the need for communication and exchange of ideas led to the establishment of expertise networks in the field of biobanking (Fig. 1). Expertise networks are networks of individual people, rather than networks of biobanks, as illustrated by the diagram in Fig. 4. Expertise networks, with their conferences and trade exhibitions have a major role in providing a forum for networking. They bring together representatives of many different biobank networks, expertise networks and vendor organizations, so they can be said to “network the networks”. As described below, expertise

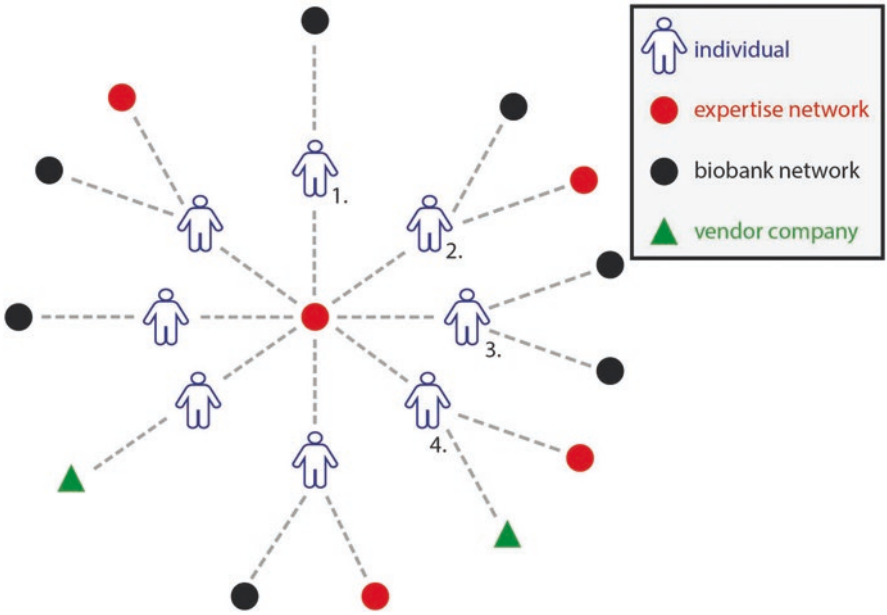

Fig. 4 Illustration of an expertise network. In this example, the individuals all belong to the expertise network represented at the centre of the diagram. Individual 1 also belongs to a biobank network. Individual 2 also belongs to a biobank network and a second expertise network. Individual 3 also belongs to two overlapping biobank networks. Individual 4 also belongs to a vendor company and a second expertise network

networks also play an important educational role, through their conferences and other activities. In addition, they support working groups that allow members to collaborate in solving problems in the field.

This section will consider three examples of expertise networks: ISBER, ESBB and 3-C-R. It will then discuss the differences, common features and synergies between these organizations.

4.1 Example 1: International Society for Biological and Environmental Repositories (ISBER)

ISBER is a good example of an expertise network. As stated on its web site "ISBER is the largest international forum that addresses the technical, legal, ethical, and managerial issues relevant to repositories of biological and environmental specimens [29]. ISBER is a professional society of individuals and organizations who share an interest in promoting consistent, high quality standards, ethical principles and innovation in biospecimen banking by uniting the global biobanking

Table 2 List of current ISBER Working Groups

Year established	Working group name
2008	Biospecimen Science
2008	Informatics
2008	Regulatory and Ethics
2009	Environmental Biospecimens
2012	Hospital-Integrated Biorepositories
2012	International Repository Locator
2013	Trans-Omics
2013	Integrated Biobanking Workflows

community. ISBER invites all sub-components of government, academia, the private sector, and manufacturers to become active participants of the society."

ISBER was created in 1999 by a group of biobanking experts from various academic, Government and commercial organizations (US NIH, US CDC, American Type Culture Collection and others). As of late 2016, ISBER is comprised of over 1100 individual and organizational members from six continents. From its inception ISBER leadership and members have been engaged in global networking to engage the biobanking community in developing and sharing information to promote biobanking standards and biospecimen science. One of the organization's first efforts was to develop ISBER's Best Practices for Biorepositories, now in its third edition and available on the ISBER web site [30]. The ISBER Best Practices have been widely adopted by biobanks in various international settings, and the fourth edition is now being developed. In addition, ISBER has created a Self-Assessment Tool [31], which as noted on the web site is designed "to assist repository operators in determining how well their repository follows the ISBER Best Practices for Repositories. The assessment is confidential and aimed at helping specimen collection centers strengthen their practices through the identification of areas in need of improvement."

ISBER's role as an expertise network is also supported by a variety of advisory committees, working groups and initiatives, which support its global research and educational mission. The working groups, in particular, are engaged in a series of initiatives, which are relevant to ISBER's role as an expertise network (Table 2). This table and discussion below are adapted from an "ISBER Corner" article published in *Biopreservation and Biobanking* in 2014 [32].

Although all ISBER Working Groups (WG) are engaged in international activities to a certain extent, two of them, the Biospecimen Science WG, and the International Repository Locator WG are particularly active in this regard and are the focus of the following discussion.

The ISBER Biospecimen Science WG was established as one of the first WGs in 2008. Biospecimens stored in biorepositories are intended to be used for biomarker identification and validation. The performance of such biomarkers greatly depends on the pre-analytical variables that can affect the down-

stream performance of samples [33]. The Biospecimen Science WG developed a biospecimen science database which includes hundreds of references, a standard biospecimen research experimental protocol, the Standard PREanalytical Code (SPREC), the Proficiency Testing program, and the Preanalytical External Quality Assurance survey tool [34]. As well identifying potential new quality control tools, and performing collaborative experimental projects on RNA and viable cell stability, this WG is engaged in various other activities. During 2014 the WG's activities included the following: (1) tissue heat stabilization studies; (2) a robustness study of clinically relevant biomarkers; and (3) the validation of biospecimen quality control markers/tools. A project on low quality RNA stability at room temperature is being launched. An experimental project on viable tumor tissue cryopreservation is being discussed, and could be the opportunity for collaboration with members from the Society for Cryobiology. In addition, close association with the Environmental Biospecimens WG is maintained in order to cross-pollinate ideas and opportunities for trans-disciplinary biospecimen science. The Biospecimen Science WG also engages in interaction and collaboration with other organizations, including pharmaceutical companies, the Human Proteome Organization (HUPO) and the International Organization for Standardization/Technical Committee (ISO/TC) 276 [35].

The International Repository Locator WG was established in 2012 to address the biorepository community's need for developing a catalog of many of the existing biobanks supported by members of ISBER, as well as other international biorepository organizations. Many of these individual biobanks and organizations already have online catalogs, but there is no central web location that allows for searching across the multiple web sites where these "locators" are hosted. The availability of a searchable, online biobank/specimen (or "resource") locator is considered a critical research infrastructure. To maximize the value of a specimen or collection, a researcher requires the ability to locate and access certain criteria associated with those specimens. Specimens may also be needed from multiple repositories in order to generate data with statistical rigor. After analyzing the results from a survey the WG distributed to the ISBER community in 2013, it was concluded that an international web resource that can be populated with basic information concerning available specimen collections needed to be established. This web resource will increase the profile of individual repositories among key stakeholders, including ISBER, researchers, funding bodies, governments and private industry. A web site has been established and the WG is in the process of populating it with relevant information. A set of simple web links to multiple biobank locators will be established in the first phase of development, followed by consideration of a more detailed international locator in a future phase.

For additional information concerning ISBER's contributions to international activities see the ISBER web site (http://www.isber.org).

4.2 Example 2: European, Middle Eastern and African Society for Biopreservation and Biobanking (ESBB)

One challenge that has inevitably been faced by ISBER, as a US-based international society, has been to provide meetings on other continents that are sufficiently frequent to satisfy regional needs. The subject of forming a European chapter of ISBER was discussed at the 2010 ISBER meeting in Rotterdam, and this was continued in an online discussion forum on LinkedIn. The LinkedIn discussion group grew rapidly to over 600 members and in response to the high level of interest a group of 35 people took the initiative to meet in Milan in late 2010 to establish a society called the European, Middle Eastern and African Society for Biopreservation and Biobanking (ESBB).

The mission of ESBB is to advance the field of biobanking in support of research relating to healthcare, education and the environment. The goals are as follows:

- Identify problems in the biobanking field and provide solutions.
- Encourage high professional standards in biobanking.
- Provide high value membership services for key actors in the biobanking field.
- Encourage participation from a wide range of repositories across the EMEA region.
- Provide a strong united voice for biobankers in the region, to influence development of their field.
- Partner with other organizations involved with, or related to biobanking.
- Encourage and support public-private biobank-related partnerships because of their scientific, medical and commercial importance.
- Promote stakeholder support for biobanking.

The first annual conference of this society was held in Marseille in 2011. Subsequently ESBB annual conferences have been in Granada (2012), Verona (2013) and Leipzig (2014). Conferences typically feature about 40 invited speakers and all have been successful in attracting audiences of 400–500 participants and 40–50 vendor exhibitors.

ESBB conferences focus on subject matter that is most relevant to biobanking in the EMEA region. To enable biobankers from emerging countries in the region to attend, a total of 17 travel fellowships have been provided so far with society, corporate and biobank sponsorship.

Working Groups established by ESBB are as follows:

- ESBBtranslate, which brings together ESBB members and pharma/biotech industry representatives in order to identify, elaborate and launch common research projects.
- ESBBperanto, which is focussed on harmonising definitions and languages in biobank databases to facilitate comparability of biomaterials and data across different biobanks and countries.

- The Enviro-Bio Working Group, which is dedicated to international collaboration on all non-human tissue and environmental samples. This is a joint ISBER-ESBB working group, as described below.
- The Africa working group aims to address the particular challenges and opportunities of biobanking in Africa.

The ESBBtranslate working group (initiated in 2012) is particularly active and is currently developing a novel biobank resource locator to help biobanks showcase their specific assets and services, and assist in particular the pharma/biotech industry with a quick-and-easy query for biobanks relevant for an industrial research setting. Over a web-based questionnaire, pertaining information is currently being collected and will shortly be made available over the ESBB website. ESBBtranslate has also established the Research Biobank of the Year Competition (RBYC) as a mechanism to promote high standards in biobanking [36].

ESBB has collaboration agreements with a variety of biobank and expertise networks as described below and has a liaison with the International Organization for Standardization/Technical Committee (ISO/TC) 276 "Biotechnology" [35].

Further information about ESBB can be seen on its website at http://www.esbb.org.

4.3 Example 3: Club 3C-R

Club 3C-R, founded in 2006, is a French private network of biobanks with today 91 biobanks and six Biobank networks. It is set up to meet expectations of people who wished to benefit from a structure dedicated to the professionalization of biobanks in order to exchange and work on the themes of collection management. Some pharmaceutical companies and equipment, consumables and instrumentation suppliers become members in order to bring a complementary vision on some specific points.

The power of Club 3C-R proceeds from two complementary elements: its members and its animator. Its animator has been involved for 20 years in the professionalization process of biobanks and brings her knowledge and expertise through solutions and tools, remaining as close as possible to the national and international actuality on biobanks. The tools she proposes to help daily operations of the infrastructures are:

- A supervision of regulation to notify the biobanks managers of changes that may impact their activities;
- A Publication of a bimonthly newsletter (Cahier 3C-R) to provide information on published articles that could be of interest to the biobanks (biobank management, quality management systems, technical processes for samples, management and use of associated data, laws, ethics). This Cahier 3C-R has already referenced more than 4500 articles since its first edition;
- The creation and release of document templates (67 already published) to help biobanks with their quality management system, according to the standard requirements (ISO 9001 and the French NF S 96-900 Standard)

- A hotline which allows to respond quickly to questions (with an average of more than 110 responses per year over the last 3 years)
- Constitution of a virtual library with around 300 articles referenced, annotated with key-words and made available;
- Close contact with authorities (ministries, certification bodies) and other expertise networks like ESBB;
- Organisation of a HUB to centralise sample requests from companies in order to foster the valorisation of biological resources.

On the other hand, the Club 3C-R members, who represent a high majority of French biobanks, contribute to the life of the Club by providing a highly professional vision through their testimony and knowledge. Moreover, given that the Club 3C-R members represent many different activities of the daily life of biobanks (Operational Managers, Medical Directors, Quality Managers, Technicians and Engineers, Computer Scientists, Lawyers, people representing legal entities), the analysis are made in a multidisciplinary form that provides pragmatic and comprehensive solutions representative of the daily management of collections. All the people involved can contribute:

- To Identify new problems which could have an impact on biobank management; this implication allows a constant update of the Club C3-R actions so they remain adequate and useful for most biobanks;
- To take part in the writing of document templates published by Club 3C-R;
- To be involved in work groups to obtain relevant solutions (e.g. the work on an information and consent document for the use of human biological resources through biobanks, a screening of the risks encountered by biobanks to help them set up necessary actions to reduce these risks, the designing of a spreadsheet template to quickly establish financial quotations for sample supplies);
- To propose services as cross audits or to share free software dedicated to the quality management system (e.g. AQ-Tools software);
- By answering surveys that highlight the position of French biobanks (the last survey focused on the impact of certification for a BRC);
- Through their participation at the annual Club 3C-R meeting, which represents a privileged place for networking, exchange, collaboration and birth of new development ideas.

All these actions have contributed to an easier development of each biobank infrastructure, and Club 3C-R has become the most important French collaborative network working on the theme of management of human biological resources, but also animal, plant and environmental biological resources.

Moreover, Club 3C-R has now become a representative institution able to take college positions (e.g. on the revision of the French standard for the BRC Quality, on the publication of the Biobank quality standard by the British NCRI's Confederation of Cancer Biobank and on the revision of the Rec(2006)4 Recommendation of the Committee of Ministers to member states on research on biological materials of human origin).

4.4 Similarities, Differences and Synergies Between Expertise Networks

Much of the activity of expertise networks is focused around an annual conference of 2 or more days where members and non-members meet to attend a variety of activities, including talks, seminars, workshops, working group meetings, poster sessions, trade show, training courses and social events. Then throughout the year, activities continue in committees and working groups via teleconference calls, and for the membership in general via email forums and the social media. While the above accounts list some of the tangible benefits of organizations like ISBER, ESBB and 3C-R, many of the benefits are intangible: these include not only the results of innumerable information exchanges across organizational boundaries, but also the fact regular in-person meetings lead to community development with links of trust and friendship that facilitate cooperation and teamwork. With so much that is intangible, it is difficult or impossible to estimate the total contribution these organizations have made over the years.

ISBER, ESBB and 3C-R all cater to people involved in a broad spectrum of biobank types, but they differ in the geographic scope of their interests and activities (Table 3). While ISBER has a global scope including all time zones, ESBB concentrates on the EMEA region (Europe, the Middle East and Africa), and 3C-R is focused on France. In this age of globalization, ISBER's role is crucial to promote global harmonization of biobanking standards and policies. However, there is also a need for attention to local and regional factors. For example, conferences must be feasible to attend, topics and discussions should be sufficiently focused on content that is locally relevant, and discussions must be in a commonly understood language (which may not necessarily be English). Some further examples of expertise networks in the biobanking domain can be seen in Table 1. Participation in such networks is generally voluntary, and participants provide financial support through membership subscriptions and conference registrations. The existence of these various expertise networks depends on this member support and provides evidence that no single expertise network meets all the different needs.

Table 3 Comparison of three different expertise networks

	ISBER	ESBB	3C-R
Geographic scope	Global	EMEA region	France
Potential for global harmonisation	+++	++	+
Global relevance	+++	++	+
US relevance	+++	++	+
EMEA relevance	+	+++	++
French relevance	+	++	+++
Conference locations	60% in USA	All in Europe so far	All in France
Convenience of conference location	Variable	Variable	+++
Language spoken	English	English	French
Convenience of language spoken	Variable	Variable	+++

As illustrated by the case studies on ISBER, ESBB and 3C-R, there are many ways in which expertise networks can work together. ESBB for example has collaborative agreements with a number of organizations, including an affiliation agreement with ISBER and memoranda of understanding with EPMA, ANRRC, KNRRC and BEDO (Table 1). These agreements cover various activities including cross-representation on leadership committees, mutual promotion, and collaboration on educational programmes. One particularly interesting way in which expertise networks can collaborate is through shared working groups. One example is the 'Enviro-Bio' Working Group which is a joint working group shared by ISBER and ESBB. Members of this working group are a particularly diverse group of people involved in studying all non-human species across the Tree of Life and from all habitats across the globe. Coordination to share biological material and data cost efficiently between countries worldwide has become an especially important issue in the light of the enforcement of the CBD's Nagoya Protocol in October 2014. As a result, transparent access benefit sharing (ABS), IPR and collection permit contract management including use of traditional knowledge (TK) in local indigenous communities, became mandatory. The Enviro-Bio working group plays an important coordinating role by virtue of the fact it links not only of ISBER and ESBB, but also members of SciColl, SPNHC, SYNTHESYS, Frozen Ark consortium, i/CBOL, STLB, KNRRC, ANRRC, BEDO and GGBN (Table 1). In this way, the Enviro-Bio working group can truly be said to 'network the networks'.

5 Biobank and Expertise Networks Compared

From the case studies reported above it is clear that biobank and expertise networks show similarities and differences. These are summarized in Table 4.

Biobank networks generally have formal organizational structures with disciplined management to ensure cooperation and maintenance of common standards across the multiple member biobanks. In contrast, expertise networks are less formal organizations, populated by volunteer members and they generally have a democratically elected leadership.

The priorities of biobank and expertise networks also show significant differences. While biobank networks aim to provide an efficient biobanking service and demonstrate cost effectiveness to their funding agencies, the main priority for expertise networks is to meet the needs of members and conference attendees who are themselves the source of expertise network funding.

As illustrated in Table 4, biobank networks at the local and regional level are focused on biobank operations, while biobank networks at the national and international level also show many of the activities of expertise networks, including the running of conferences, educational activities and working groups. So there is

Table 4 Comparison of biobank networks and expertise networks

	Local and regional biobank networks	National and international biobank networks	Expertise networks
Leadership	Institution-led	Institution-led	Often member-led and democratic
Funding	Grants	Grants	Member subscription, Conference registration
Main priorities	Provide biobank services that bring research benefits	Increase the effectiveness of member biobanks and networks	Meet the needs of members and conference attendees
	Demonstrate cost effectiveness to funding agencies	Demonstrate cost effectiveness to funding agencies	Advance the field of biobanking
		Advance the field of biobanking	
Roles			
–Biobank operations	Yes	Yes	No
–Adminstrative role	Yes	Yes	No
–Funding of biobank services	No	Yes	No
–Conferences	No	Yes	Yes
–Website and social media	No	Yes	Yes
–Develop educational material	No	Yes	Yes
–Provision of research tools, catalogues	No	Yes	Yes
–Working groups	No	Yes	Yes
–Advocacy	No	Yes	Yes

a great deal of overlap between the activities of larger biobank networks and expertise networks. In these areas of overlap there is the risk that efforts may be duplicated, but at the same time there is the opportunity for sharing out tasks and for collaboration.

6 Conclusions

One shared priority for larger biobank networks and expertise networks is to advance the biobanking field and to overcome the obstacles that hinder efficient biobanking operations at all levels. Barriers to transnational biobanking operations are of

particular concern at this time of increasing global interdependence, since these barriers block research to address major global threats like disease epidemics, climate change and the biodiversity crisis [37]. Major barriers include: (1) incompatible technical standards for sample collection and processing, (2) incompatible ethical standards relating to informed consent and privacy protection, (3) lack of information about available resources, and (4) lack of cooperation due to concerns about exploitation of national resources [38]. To overcome these barriers as quickly as possible, biobank networks of all kinds need to communicate with each other and collaborate to find solutions [37].

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Networking Biobanks Throughout Europe: The Development of BBMRI-ERIC

Eero Vuorio

Abstract The purpose of this chapter is to summarize the process towards establishment of the pan-Eurovpean Biobank infrastructure BBMRI (Biobanking and BioMolecular Resources Research Infrastructure) as a legal entity under the ERIC regulation. The chapter gives an overview of the science case for collaboration of biobanks and describes early attempts to bring harmonization, cohesiveness and interoperability to the field, and discusses the possibilities opened up by the ESFRI (European Strategy for Research Infrastructures) process. After inclusion of biobanks on the first ESFRI Roadmap of 2006, BBMRI became one of the first European Research Infrastructure projects to receive funding from the European Commission (EC) from February 2008 onwards. The 3-year EC-funded Preparatory Phase (BBMRI-PP) came to its end in January 2011. During this time BBMRI grew into a 54-partner consortium with 224 associated organizations (largely biobanks) from 33 countries, making it the largest research infrastructure project in Europe. During the Preparatory Phase the concept of a functional pan-European biobank was formulated and was presented to Member States and Associated States of the European Union for approval and funding. The plan was approved by a total of 16 EU Member States and Associated States, which became founding members and observers of BBMRI-ERIC legal entity in late 2013.

Keywords BBMRI • Biobank • Biorepository • Biological sample collection • Research infrastructure

This chapter is dedicated to the memory of Leena Peltonen-Palotie and David Cox, who both made major contributions to the BBMRI concept.

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1 Origins of European Biobanking

The tradition of sample collection, particularly collection of formalin-fixed paraffin-embedded tissues in pathology departments, within the health care system started in early to mid-1900s. Initially these samples were used for diagnostic purposes, but their storage for extended periods was justified by the need of material for follow-up of disease progression, efficacy of treatment regimens and for quality control. In many countries the requirement for extended sample storage is based on national legislation, which may also set limits for minimum (and maximum) storage of patient-derived samples. Biomedical research on human diseases has also resulted in collections of patient-derived blood and tissue samples, cell lines and other kinds of biological material. Initially such collections have been in the custody of individual principal investigators, but are gradually finding their home in national biobanks. On the other hand, some countries had initiated systematic collection of samples and data from population cohorts already in the 1950s and 1960s particularly in Northern Europe. Although the three types of "historical" collections of human biological samples were not called biobanks at the time of collection, they fulfil most of the criteria of biobanks. One important problem of such early collections is lack of written informed consent, as the concept of informed consent did not exist until much later. Participants were simply informed of the purpose and voluntary nature of the study and if they participated they had given their consent to participate. The different historical backgrounds of the three types of sample collections also contribute to the considerable heterogeneity of early biological sample collections in Europe.

2 Biobanks Become Recognized as Valuable Sources for Genetic Epidemiology and Research on Disease Mechanisms

With the development of molecular genetics and high-throughput tools for analysis of large numbers of human samples, the value of old sample and data collections was discovered in the 1990s. Several projects in Europe and beyond demonstrated that biobanks serve as key resources for epidemiological studies.

Towards the end of Framework Program 5 (FP5) the European Commission tested a new two-stage funding instrument called Integrated Project to support very large research projects. One of the three Integrated Projects that in 2001 was selected for funding in the Health domain was GenomEUTwin (Genome-wide analyses of European twin and population cohorts to identify genes in common diseases) [1] led by Leena Peltonen-Palotie. Supported by a global scientific community participating in the P3G (Public Population Project in Genomics) project, the GenomEUTwin project (2002–2006) was among the first to demonstrate the feasibility of effective cross border collaboration (beyond Europe) on very large numbers of samples from

twin pairs. Development of novel IT solutions made it possible to link federated biobanks and databases in different countries, and prepared the way towards a pan-European biobank [2].

In 2000, the European Commission invited representatives from Member State funding agencies to a Forum of Genomes Research Managers to discuss way of better coordination of national genome research programs. The Commission provided financial support to a follow-up Strategic Accompanying Measure, COGENE (Co-ordination Activity in the field of Genomes Research) in 2002–2004, which marked one of the first pan-European attempts to initiate an inventory of existing sample collections (population cohorts) in Europe, and at the same time encourage new initiatives in population genomics.

By the turn of the millennium the word biobank had been adopted to denote a repository for (human) cells, tissues, blood or DNA, which can be linked to data and information on the respective donors, particularly on their health and life style. Under EU's FP6 and FP7 a number of coordination actions, such as PHOEBE (Promoting Harmonisation of Epidemiological Biobanks in Europe) in 2006–2009 [3], ENGAGE (European Network for Genetic and Genomic Epidemiology) in 2008–2012 [4], GEN2PHEN (Genotype-To-Phenotype project) in 2008–2013 [5] and BioSHaRE-EU in 2011–2016 [6] were funded. These and many other projects worked on development of tools and methods and harmonizing biobanking activities. Under FP7 a novel public-private-partnership IMI (Innovative Medicines Initiative, www.imi-europe.org) also funded several biobank-related projects. The projects listed above occurred in parallel to development of the BBMRI concept during the ESFRI process and subsequently during the Preparatory Phase, and in most cases included partners who were also involved in BBMRI-PP.

Through systematic research on disease mechanisms biobanks were gradually realized as key resources for disease stratification (molecular subtyping of diseases), a cornerstone for personalized medicine. They also play an important role in identification of new targets for therapeutic interventions especially drug development and for companion diagnostics. Large-scale genomics projects aimed at understanding the interactions of genes, environment, nutrition and lifestyle which typically rely on large sample sets and databases present in biobanks.

3 Towards Organizing the Biobanking Community in Europe

By the 1990s the global scientific community had become fully aware of the need to collect very large sample sets from several different biobanks in order to start resolving the genetics of complex common diseases. The different EU-funded projects listed above clearly brought the community together. Also biobanking scientists sought for an organization of their own, which resulted in founding of ISBER (International Society for Biological and Environmental Repositories)

already in 1999. ISBER was not, however, an international biobank, but primarily a professional society of individuals (and organizations) providing an international forum addressing practical issues related to repositories of biological specimens as described Hewitt in Chap. 7 of this volume.

P^{3}G (Public Population Project in Genomics and Society) was founded in Canada in 2003 as a global not-for-profit consortium that provides the international research community with access to the expertise, resources and innovative tools for health and social sciences research. Many European scientists involved in establishing BBMRI had already been active in P^{3}G (Public Population Project in Genomics and Society). An important activity of P^{3}G was cataloguing of human epidemiological sample collections. The P^{3}G questionnaire was later adopted in a slightly modified form by BBMRI Preparatory Phase to develop the first inventory of European population-based and clinical biobanks that may serve as building blocks of BBMRI-ERIC. The large FP7-funded European project ENGAGE also collaborated with P^{3}G, to produce a Consortium Catalogue, a repository of standard information describing ENGAGE cohorts available in the P^{3}G Observatory web site [7].

World Health Organization (WHO) and the Organization for Economic Co-operation and Development (OECD) also became interested in international cooperation of Biological Resource Centres. OECD drafted its best practice guidelines for biological resource centers [8, 9] with an aim to establish a Global Biological Resource Centre Network (GBRCN).

In Europe, the European Science Foundation (ESF) and its Standing Committee of European Medical Research Councils (EMRC) were actively following the developments in biobanking in their member countries and supported meetings of the biobanking community as described below.

4 The European Strategy for Research Infrastructures (ESFRI) Provides a Potential Instrument to Establish a Pan-European Biobank

Parallel to the self-organization of the European biobanking community through large, often EU-funded projects, another important development started in Europe in 2002: the European Strategy Forum on Research Infrastructures (ESFRI) process. The ESFRI was mandated to “support a coherent and strategy-led approach to policy-making on research infrastructures in Europe, and to facilitate multilateral initiatives leading to a better use and development of research infrastructures”. This process finally brought recognition to key infrastructures in the biological and medical sciences (BMS) domain in par with those in the natural sciences domain, especially physics and astronomy, as well as social sciences and humanities.

ESFRI embarked on a complex methodology to produce the first European Roadmap for Research Infrastructures. One of the three dedicated Roadmap Working Groups (with more than 70 representatives from all EU countries) was the

Working Group on Biological and Medical Sciences (BMS) chaired by Ruth Barrington (IE). Within the remit of the three Roadmap Working Groups, 15 Expert Groups with a total of more than 150 members were created in the summer of 2005 to cover specific areas within the three domains. In the BMS domain three Expert groups were established: (1) Genomics, proteomics, bioinformatics and biology; (2) Clinical and translational research, imaging and radiation; and (3) Biodiversity and environment.

More than 200 proposals were received for the first European Research Infrastructure Roadmap. Each proposal was analyzed for its (pan-European) science case and for concept and maturity, first by an Expert Group, then by the applicable Working Group. For the biobanking field, two different proposals were received, one for basic science domain and another for the clinical/translational research domain. The evaluation of the proposals submitted to ESFRI by the different scientific communities started in August 2005. This involved feedback to the proposing scientists proposing a single biobank infrastructure proposal. The scientists behind the proposal came together and drafted one joint proposal for a Research Infrastructure for Biobanking and BioMolecular Resources, which was subsequently recommended by the two respective Expert Groups to the BMS Working Group for inclusion on the Roadmap. The end result of this long process was the inclusion of BBMRI on the first European Research Infrastructure Roadmap of 2006 [10].

Parallel to the European road mapping process a number of national initiatives to establish research infrastructure roadmaps were started. Soon after the publication of the first ESFRI Roadmap in 2006 biobanks appeared also on national roadmaps in several European countries with long tradition of collecting population cohorts, Finland, Sweden, the Netherlands being among the first. In some countries (e.g. Iceland and Estonia) and regions (e.g. Styria) large biobanking projects had already been established indicating national and regional interest in systematic collection and storage of biological samples and data for research purposes.

5 Building the Concept of a Pan-European Biobank with BBMRI Preparatory Phase Funded by the European Commission

Creation of the 2006 ESFRI Roadmap in 2 years was a major achievement which brought a new kind of momentum to European science policy and scientific community, and brought new concrete meaning to the concept of European Research Area. For the scientific communities a status on ESFRI Roadmap was a major encouragement as it also meant eligibility to apply for a Preparatory Phase (PP) funding from the European Commission under the Seventh Framework Programme. To write such an application the European biobanking community had to organize itself in a more concrete way in order to come up with a work programme towards realizing the

concept of a pan-European biobank. This preparatory work was supported by European Science Foundation (ESF) which sponsored scientific meetings in the area. In a meeting in Amsterdam on December 7–8, 2006, titled Population Surveys and Biobanking, a number of recommendations for European Biobanking and Population Surveying were made, which could be seen as an early version of the work package structure of the future BBMRI-PP work program [11]. Key drivers of the process, professor Leena Peltonen-Palotie from Finland, professor Gert-Jan van Ommen from the Netherlands and professor Kurt Zatloukal from Austria, agreed on the division of tasks. Kurt Zatloukal became the coordinator of the PP application, Leena Peltonen-Palotie the chair of the Steering Committee and Gert-Jan van Ommen the chair of the Governance Board and Scientific and Ethical Advisory Board. The Work Package structure adopted for BBMRI-PP will be discussed below.

Work towards the application also involved contacting EU Member States for their participation in the PP. A meeting of potential partners and stakeholders was organized in Vienna on March 17, 2007. Widespread commitment of Member States and Associated States was remarkable: with 52 partners and some 200 associated partners representing 34 countries (16 partner countries: Austria, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Malta, Norway, Spain, Sweden, the Netherlands, United Kingdom; and 18 associated countries: Australia, Belgium, Bulgaria, Canada, Cyprus, Czech Republic, Faroe Islands, Israel, Latvia, Luxembourg, Martinique, Poland, Portugal, Romania, Saudi Arabia, Slovenia, Switzerland, Turkey) BBMRI-PP became one of the largest EU-funded coordination projects. In 2007, the EC granted 5 MEUR to fund the 2-year Preparatory Phase of BBMRI which served as a real trigger towards planning of BBMRI-ERIC as we know it today. Since the beginning of the Preparatory Phase on February 1, 2008, the number of partners grew to 54 and associated organizations to 224 by the end of the Preparatory Phase on January 31, 2011. The associated organizations included biobanks, research institutions as well as several ministries and funding organizations.

6 Activities of BBMRI-PP

In the BBMRI kick-off meeting in Hinxton in February 2008, professor Eero Vuorio was elected as the executive manager of the PP and the tasks of the executive management office were divided between Graz, AT (at Kurt Zatloukal's home university) and Turku, FI with Michaela Mayrhofer and Heli Salminen-Mankonen working as full time project managers. From the beginning it was realized that BBMRI's main task, provision of access to biological samples and data that properly represent the diversity of European populations and diseases, can only be achieved by a distributed research infrastructure with operational units ("National nodes") in most, preferably all European Member States. Considering the national character of both biobanks and the related health and registry data and the heterogeneity of their custodianship a distributed

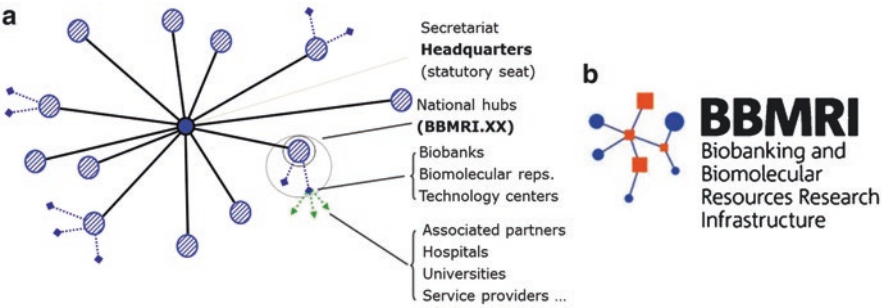

Fig. 1 Schematic presentation of the distributed hub-and-spoke structure of BBMRI (**a**) and BBMRI logo (**b**). A distributed architecture was adopted for BBMRI to accommodate the national character of biobanks and the related health and registry data and the heterogeneity of their custodianship

architecture was adopted as it would allow samples and data to be stored at national level for integration at European level (Fig. 1). The distributed hub-and-spoke architecture had been graphically designed already for the GenomEUtwin project; the same graphic profile was subsequently adopted as the central element for the logo design for BBMRI.

In its application for Preparatory Phase funding BBMRI expressed as its main aim as "to build a coordinated, large-scale European infrastructure of biomedically relevant, quality-assessed sample collections, to enhance therapy and prevention of common and rare diseases, including cancer". Biobanking was considered to represent a unique European strength, although without adequate coordination the valuable and irreplaceable national collections were judged to suffer from underutilization due to fragmentation. To achieve these goals, it became obvious that harmonization, standardization and interoperability became key words during the execution of the work programme of BBMRI-PP. The "pilot" studies conducted by participating scientist summarized above under Sect. 2 had clearly demonstrated the need for synergy to gain statistical power and economy of scale to make it possible to understand the association between subtypes of common diseases and variations in genotype, phenotype, and lifestyle. To reach these goals it was realized from early on that a well-functioning bioinformatics infrastructure must be an integral part of BBMRI.

7 Work Package Structure

In the application for BBMRI-PP funding, a structure of seven work packages reflecting key activities to build a biobanking infrastructure was envisaged (Table 1). This structure has remained essentially unchanged through the interim and the construction phases and now serves as the basis for the Work Program and operations of BBMRI-ERIC. Many national BBMRI nodes have also adhered to the same work package structure, sometimes with minor modifications.

Table 1 Work Package structure of BBMRI-PP

Work packages (WP)	WP leaders
WP1: Management and Coordination	K. Zatloukal (AT) coordinator; M. Yuille (UK) deputy coordinator; E. Vuorio (FI) excutive manager; M. Pasterk (global interactions)
WP2: Population-based Biobanks	L. Peltonen (FI)/M. Perola (FI), A. Metspalu (EE)
WP3: Disease-orientated Biobanks	E. Wichmann, (DE), T. Meitinger (DE)
WP4: Biomolecular Resources and Molecular Tools	U. Landegren (SE), M. Taussig (UK)
WP5: Database harmonisation and IT-infrastructure	J-E. Litton (SE), M. Fransson (SE)
WP6: Ethical, Legal and Societal Issues	A. Cambon-Thomsen (FR)
WP7: Funding and Financing	G. Dagher (FR), J. Ridder (NL), C. Bréchot (FR)

7.1 Work Package: Governance and Management

The Governance and Management structures adopted for BBMRI-PP were as simple as possible for a project of over 270 partners and associated partners. Due to the very large size of the project, most of the important decisions were mandated to the *Steering Committee* consisting of Work Package leaders and the Chairs of the Governing Council and Scientific and Ethical Advisory Board. The Steering Committee was variably chaired by Eero Vuorio and Kurt Zatloukal from the Coordination office. The Governing council comprising all partners and associated partners only met twice, in Florence, IT on April 18, 2008, and in Brussels on March 25, 2009, to give advice to the Steering Committee and the Coordination Office. Dissemination of information between the Steering Committee and the Governing Council occurred primarily through the BBMRI-PP intranet site.

The *Scientific and Ethical Advisory Board (SEAB)* chaired by Gert-Jan van Ommen comprised ten distinguished scientists, David Cox, Howard Cann, Bela Melegh, Mark Daly, Jean-Jacques Cassiman, Bartha Knoppers, Lyle Palmer, Klaus Lindpaintner, Karima Boubekeur, and Yusuke Nakamura. The SEAB had three meetings where they were presented reports from the Work Packages in Florence (2008), Brussels (2009) and in Amsterdam (2010). In addition to their encouraging support to BBMRI-PP, the SEAB also gave valuable advice, particularly on the scientific focus and the importance of outcomes, interaction with industry and informed consent. The SEAB consistently also expressed their concern about lack of sustainable funding to BBMRI. The SEAB is to be specifically acknowledged for providing ideas for the concept of Expert Centers for industry-academia collaboration.

A separate *Stakeholder Forum* was also set up for BBMRI-PP chaired by Michael Griffith from the Irish Platform for Patients' Organizations, Science

and Industry (IPPOSI). Close interaction with the European publics had been considered essential for the success and acceptability of BBMRI-ERIC. Comprehensive consultation was conducted covering patients, clinicians, funding organizations, associated project partners, industry, users and the general public. The Stakeholder Forum organized meetings and workshops providing information on the use of the BBMRI resources and on the value derived from participation, thus enabling stakeholders to formulate informed viewpoints on biobanking. A Patient Consultation Document "Basic Principles for Patient Participation in BBMRI" was developed and has been officially endorsed by several patient organizations.

An important task of BBMRI-PP was to create a draft governance structure, Statutes and Business Plan for the future BBMRI-ERIC legal entity. Also here the aim was to create a simple, functional governance model which would accommodate for the growing membership and infrastructure activities. The basic idea was to make best use of governance structures of existing intergovernmental organizations rather than starting to reinvent the wheel. The governance of European Molecular Biology Laboratory (EMBL) with its headquarters in Heidelberg, four outstations and a number of partnerships in different Member States was well-known to several partners and served as a model for a well-functioning federated organization. Subsequently the Governance structure and the Statutes of BBMRI-ERIC are based on the ERIC regulation and bear clear resemblance to that of EMBL. As stated earlier, a federated structure was the only possible solution for BBMRI-ERIC since the participating biobanks and registries remain in Member States. The Governance structure of BBMRI-ERIC is illustrated in Fig. 2.

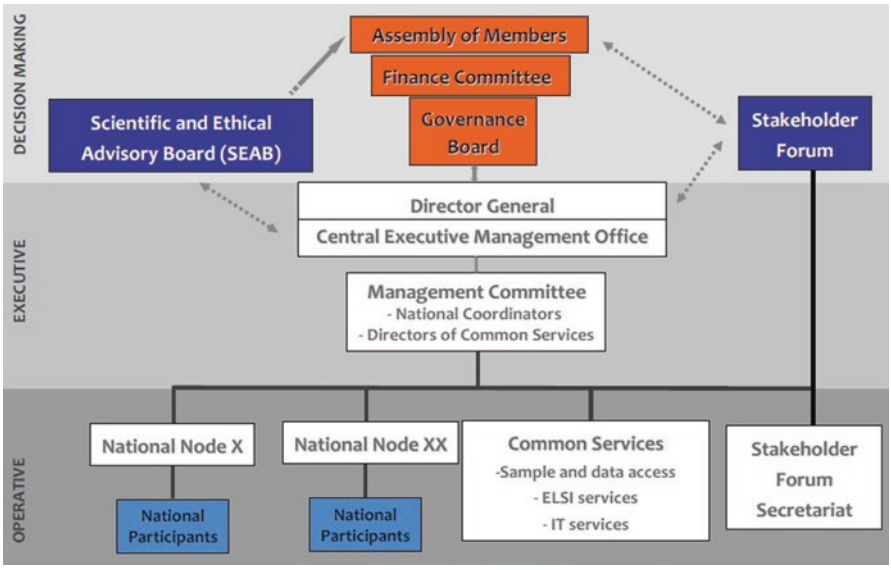

Fig. 2 The proposed governance structure for BBMRI-ERIC

7.2 Work Packages 2 and 3: Catalogues of European Biobanks

From the beginning it was clear that the future BBMRI infrastructure would provide access to the sample and data collections of BBMRI Partner Biobanks, which will physically remain in the Member States. Together with the BBMRI-PP management team, WP2 and WP3 had created the first version of the step by step access policy to human biological samples and associated data to be implemented in the future BBMRI-ERIC. Access to the federated infrastructure was to be based on scientific excellence of the proposed project as determined by an independent peer review and on ethical review of the research project proposal. To achieve this goal, an early task of BBMRI-PP was to produce an inventory of the major existing population-based and clinical or disease-orientated biobanks in Europe. Using questionnaires based on those developed by the international population cohort organization P3G, information was collected on the type and quality of collected samples and data, standardization of procedures, IT solutions as well as governance structure, funding, and legal and ethical issues of catalogued biobanks [12]. Data obtained from the survey can be accessed through a searchable catalogue at the BBMRI-PP/BBMRI-ERIC website.

It was also considered important that BBMRI provides free access to documents, Standard Operating Procedures (SOP's) and best practices developed by BBMRI. Review of SOPs that had been used in biobanks and related research projects showed several different standards, SOPs, and internal guidelines had been in use, although several official guidelines had recently become available from National Cancer Institute, OECD, ISBER and IARC (International Agency for Research on Cancer). WP2 and WP3 worked towards establishment of common detailed SOPs based on the OECD [8, 9] and IARC guidelines [13] and the work carried out by Molecular Medicine Ireland [14]. This led to a useful comparison chart of the various biobanking-related guidelines.

Another important task was to ensure that the source of samples and data are appropriately acknowledged. This turned out to be a long process which finally led to the development of the Bioresource Research Impact Factor (BRIF) concept and publication of a guideline to standardize the citation of bioresources in journal articles [15].

The BBMRI-ERIC Business Plan [16] summarizes much of the work carried out during the Preparatory Phase including the planned access process to human biological samples and identifiable medical data in a way compliant with a variety of ethical and legal requirements, such as the Oviedo Convention (ETS 164), the Helsinki Declaration, the OECD Guidelines for Human Biobanks and Genetic Research Databases (HBGRD) or the Directive 95/46/EC on the Protection of Personal Data. The access procedures of BBMRI-ERIC to human biological samples and medical data were to consider the following principles:

- No information related to individuals and their samples can be made accessible by internet; only access to coded and aggregated data can be provided through the BBMRI-ERIC web-portal,

- Access to samples and medical data can only be provided in the context of a specific research project in accordance with the terms of the consent given by the donor,
- The research project has to meet the criteria of scientific excellence (based on scientific review) and has to be approved by an ethical review board, and
- All procedures have to protect the privacy of sample donors.

Optional BBMRI-ERIC research services (Common Services), such as ethical, regulatory, and legal advice, data collection and transportation, sample processing, data analysis, and planning of prospective cohorts could thereafter be utilized and specified on a project by project basis. Noteworthy, the establishment of high quality research collaboration was considered the preferred format for access. There is no obligation for BBMRI-ERIC Partner biobanks to provide access to a specific research project if the terms are not acceptable.

7.3 Work Packages 4–6: Models for Common Services

During the Preparatory Phase it became obvious that harmonization, standardization and interoperability of European biobanking requires a series of BBMRI-ERIC Common Services to provide the biobanking community and biobank users with top-level expertise, services and tools in specific areas of biobanking. It was envisaged that Common Services are jointly funded by BBMRI-ERIC and the Member State(s) hosting the facility. Decisions on the location of Common Services were to be based on open calls and subsequent decisions by the BBMRI-ERIC Assembly of Members based on scientific excellence and cost efficacy as part of the Work Program jointly funded by the Members. In addition to actual biobanking activities common Services were envisaged for BBMRI-ERIC in the following areas:

Biomolecular tools and resources. During the Preparatory Phase a review was performed on existing resources for affinity reagents and other biomolecular resources as analytical tools applicable to biobanking. This led to a new community standard of affinity reagents (MIAPAR), designed to tackle the problems of scattered information and imprecise descriptions and to facilitate database implementation [17]. In addition, a new database for molecular methods (MolMeth) was established, providing best practice based protocols for molecular analyses of different types of samples [18]. The aim is to establish a continuously updated European network of service providers of relevant analytical technologies for measuring and imaging nucleic acids, proteins, metabolites, etc.

Database harmonization and IT-infrastructure. A key to the huge amount of biological, clinical, epidemiological and behavioural data is a well-functioning and reliable information management system to maintain unique and secure coding systems for specimens, subjects and biobanks. Subsequently, coordination and implementation of the interoperability of the existing and new biological databases of biobanks was seen as a key role of BBMRI-ERIC Common IT Service. Such an IT-infrastructure was to consist of a network based on the hub-and-spoke topology

to connect the different nodes, which are geographically spread through Europe, connected via the national or regional hubs. Common IT Services were to connect the entire network of National Nodes, Common Services, individual biobanks, users and observers into a single virtual structure, preserving on one hand privacy and autonomy, and supporting communication and collaboration on the other hand.

Harmonization of ethical, legal and societal issues (ELSI). During the Preparatory Phase analysis on the ethical, social and legal issues of the infrastructure resulted in a conceptual paper on ethics related policies for biobanks and biomolecular resources. Bovenberg [19] proposed a WIKI+ platform for legal aspects for uploading and validating existing legal documents in use in BBMRI-ERIC Member and Partner countries which is now available through the BBMRI-ERIC web site.

For efficient running of the BBMRI-ERIC ELSI Common Services each National Node is expected to designate a National ELSI Representative to participate in the ELSI Common Service activities and to interface with National Institutions, Biobanks and BBMRI-ERIC. The ELSI Common Services was to include a "Hot Line" to respond to ethical issues raised by users and a platform that provides access to existing ethical and legal frameworks for the exchange of human biological samples for research use in Europe. Training of biobank managers and ethics and legal officers was also considered an important activity.

7.4 Private Sector Access to Biobanks

Three types of users from private sector, each one interested in specific facilities provided by BBMRI were identified: pharmaceutical industries, diagnostic industries and biotechnology industries. Therefore, establishment of an international network of "Expert Centers" was proposed by SEAB of BBMRI-PP to facilitate international research collaborations by reducing the need for sample shipment and allowing primary data and value generation from biological resources to remain in the country of origin. According to the concept, BBMRI-ERIC affiliated Expert Centers are not-for-profit entities that represent a novel public-private partnership model that integrate pre-competitive public and private research and development activities by providing not only access to biological samples and medical data but also to the broad spectrum of medical and scientific expertise related to the samples, data, and their analysis [20].

7.5 Education and Training

One of the objectives of BBMRI-PP was to plan a European Master/PhD curriculum for Biobanking Management and facilitate other types of education and training in biobanking. The European curriculum is currently tested in Lyon, France, to be later spread out over several education centers in Europe. BBMRI-ERIC will play a critical role in establishing and coordinating these programs. Industry has expressed their high interest in these training activities. Through the EMTRAIN

project of the Innovative Medicines Initiative (IMI) BBMRI-ERIC is contributing to a new education and training vision for pharmaceutical R&D, especially in biomarker development.

8 Development of BBMRI-ERIC National Nodes

The enthusiasm about the development of the BBMRI concept was beautifully illustrated by the development of National Nodes already during the progression of the Preparatory Phase. The important role of National Nodes in providing a common access portal to biobank resources, facilities and expertise available in Member States has been recognized. National biobanking communities comprising universities, hospitals, research institutions and resource centres were reorganized under the BBMRI banner, often following the same WP structure as was in place for BBMRI-PP. National Coordinators were nominated to lead the development at national level.

Work on establishment of National Nodes proceeded so fast that the first meeting of BBMRI National Coordinators was organized in Amsterdam on February 10–12, 2013, 10 months before the official establishment of the BBMRI-ERIC legal entity. Thirteen National Nodes were represented by their coordinators or deputies (Austria, Czech Republic, Estonia, Finland, France, Greece, Italy, Latvia, Malta, the Netherlands, Norway, Spain, Sweden). Also the newly funded BBMRI-LPC (Large Population Cohorts) project was appropriately represented, as the aim of this FP7-funded "infrastructure-I3" project was to support the future BBMRI-ERIC in providing access to population biobanks of BBMRI-ERIC and thereby providing a real test bed for organizing scientific and ethical evaluation of research projects and the subsequent access of qualifying projects to BBMRI-ERIC-associated biobanks.

Following the BBMRI-PP tradition, the National Coordinators meeting focused on information exchange and identified a number of important areas for future collaboration. These were further discussed informally in other European biobank meetings/conferences in the second half of 2013; notably the BBMRI-ERIC Kick-off Meeting in Graz on September 26–27 and the HandsOn Biobanks Meeting in den Haag on November 21–22. After the establishment of BBMRI-ERIC, the National Coordinators meetings have become an official part of the Governance structure.

9 End of the Preparatory Phase Is Followed by a Long Interim Phase to Establish BBMRI-ERIC as a Legal Entity

In the original application and grant agreement the duration of BBMRI-PP was 2 years. However, during these 2 years it became clear that more time is needed to reach agreement on the Governance structure and financing of

BBMRI-ERIC. Through two amendments, the duration of BBMRI-PP was extended to 3 years. When the Preparatory Phase came to its end on January 31, 2011, the BBMRI-PP Steering Committee agreed that the current Steering Committee will continue to function as an interim governing body of BBMRI and the current Coordinator as the interim Coordinator until the Preparatory Body described in the Memorandum of Understanding (see below) was established.

Selection of host country for the BBMRI-ERIC legal entity had been done already during the Preparatory Phase. Ministries of BBMRI-PP partner countries received an offer from the Austrian minister for Science and Research, for Austria to serve as a host country for of BBMRI-ERIC. The matter was discussed in a Steering Committee meeting. No other formal offers were made and Austria was subsequently selected as the host country.

9.1 Involvement of Member State Ministries

The Statutes and Business plan for BBMRI-ERIC were produced during the Preparatory Phase with limited commitment of the ministries of potential member countries. Therefore, the procedure to agree on the critical issues of the Statutes (financial contributions towards joint budget, voting rights, language issues etc.) and to decide on the legal entity had to include a process where mandated ministerial representatives were involved. Towards this goal, a Memorandum of Understanding (MoU) was drafted where Member States expressed their aim to establish BBMRI as an ERIC and become Members of BBMRI-ERIC. By December 2011, 13 countries (Austria, Bulgaria, Czech Republic, Estonia, Finland, Greece, Italy, Latvia, Malta, the Netherlands, Norway, Spain, Sweden) had signed the MoU, and a BBMRI Preparatory Body was established comprising representatives of Ministries and chaired by Dr. Hemma Bauer from the Austrian Ministry. Professors Zatloukal and Vuorio served as experts in the Preparatory Body explaining the work conducted by BBMRI-PP. It took eight meetings and about 2.5 years from the BBMRI Preparatory Body to reach agreement on the Statutes and the BBMRI-ERIC Governance structure. During this time period the MoU had been signed by another eight countries (Belgium, France, Germany, Ireland, Luxembourg, Poland, Switzerland, and Turkey). The work of Preparatory Body also included unofficial consultations of the EC by the Austrian Ministry and the Statutes writing group about the acceptability of the Statutes from the perspective of the ERIC regulation.

9.2 The ERIC Application

The application for ERIC status was a two-stage process. The first application was submitted to the European Commission on July 31, 2012 and the Commission's reply came on November 21, 2012. A lot of detail that had been added to the draft

Statutes after long debates by the Preparatory Body was removed by the Commission and transferred to rules of procedures.

The excitement of having reached a consensus on all key issues of setting up BBMRI-ERIC was reflected by the decision of the Austrian Ministry and the Preparatory Body to initiate organization of the Inauguration Ceremony of BBMRI-ERIC. A high-level inauguration ceremony was organized by the Austrian ministry and the BBMRI community in Graz on September 16, 2013. Two other biobank-related events were organized in conjunction with the inauguration: the International Biobanking Summit II (IBS-II) and the first Forum of the BBMRI-LPC project.

10 Establishment of BBMRI-ERIC

On December 3, 2013, 3 days after publication of the Statutes (dated November 22, 2013) in the Official Journal of the European Union on November 30, 2013, BBMRI was officially awarded the Community legal status of a European Research Infrastructure Consortium (ERIC).

During the interim phase the Preparatory Body had realized that establishment of BBMRI-ERIC also needs the key personnel to be in place by the beginning of 2014. A search committee was appointed by the Preparatory Body to plan and implement the selection process of the first Director General for BBMRI-ERIC, followed by a similar process to identify the first Administrative Director. These processes proceeded via drafting of job descriptions for the application process and evaluation criteria to short listing of the applicants based on the curricula vitae, interviews and finally presentation of the top candidates for both positions to the Preparatory Body. Professor Jan-Eric Litton from Sweden was subsequently nominated as the first Director General and Markus Pasterk from Austria as the first Administrative Director first by the Preparatory Body and finally by the Assembly of Members of BBMRI-ERIC in its first meeting. By that time 12 EU Member States (Austria, Belgium, Czech Republic, Estonia, Finland, France, Germany, Greece, Italy, Malta, the Netherlands and Sweden) had completed the national process to commit to full membership and four other countries (Norway, Poland, Switzerland and Turkey) as well as the international organization IARC to the status of an observer.

11 BBMRI-PP in Retrospect

Overall the Preparatory Phase of BBMRI can be considered a success. All milestones and deliverables as outlined in the Description of Work were reached and approved by the European Commission. Some additional deliverables, such as the development of the Expert Center concept were an over performance.

In addition to the positive evaluation of BBMRI-PP by the Commission, BBMRI also received a favorable assessment by the ESFRI Expert Panel in 2014 [21]. Thus

BBMRI-ERIC became one of the first ERICs to be implemented, and one of the largest. The facts that the membership of BBMRI-ERIC covered both the largest and the smallest Member States and showed a reasonable good geographical distribution were looked upon very positively. Another indicator of success of the BBMRI concept was the constantly increasing interest to join BBMRI-PP, and later BBMRI-ERIC.

The main weakness of the BBMRI-PP scheme was the overly optimistic estimation (originally 2 years) of the timeline to organize and connect biobanks across the national borders and to commit Members States towards the Construction Phase. When the Statutes and the Governance structure developed during the Preparatory Phase were presented to the Member State ministries with very divergent decision making processes, it took over two and a half years to find agreement. The fact that ERIC was a new legal entity in Europe and establishment of BBMRI-ERIC took place in financially difficult times made the process even more difficult. This also explains why some countries have not yet been able to join BBMRI-ERIC despite their active participation in the Preparatory Phase and Preparatory Body.

A number of bottlenecks were identified during the Preparatory Phase. The most important challenge was created by the heterogeneity of the status of current European biobanks, typically linked to hospitals, universities, different research performing institutions, and national health institutes. The ownership of the biobanked samples was sometimes unclear as was their availability for biomedical research, governed by consent forms, national ethical review systems, and national legislation, which differed from one country to another. Also the molecular, clinical and life-style data attached to biobanked samples were in heterogeneous formats, usually gathered in the respective national languages. Interoperability of the existing data was a major challenge. All these factors form obstacles on the path towards smooth transnational access to biobanks. The BBMRI-LPC project has been testing the access procedure and has shown that transnational access is possible, but still faces many national and institutional regulations that slow down the process of accessing biobanks.

At the time of writing, BBMRI-ERIC has been in existence for a little over 1 year. The first work program has been prepared along the lines outlined in the Business Plan and the central coordination office is now housed in a new office building in Graz, Austria. The Assembly of Members and the Management Committee have been working hard to remove the remaining obstacles and the pan-European biobank BBMRI-ERIC has become a reality.

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P^{3}G: Towards an International Policy Platform for Population Genomics

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Abstract The widening scope of biobanking activities in recent decades necessitates purposeful networking that aggregates international efforts and expertise in population health research. To this end, the Public Population Project in Genomics and Society (P^{3}G) has been able to streamline the process of establishing, operating and supporting the work of international biobanks since 2004. Since its inception, networking has been a central focus in all P^{3}G initiatives. This chapter discusses P^{3}G's networking experiences and its evolving goals that have allowed for collaborative tool building and innovation in international biobank research. As a direct result of its networking initiatives, P^{3}G (1) facilitates innovation, (2) improves data sharing and accessibility, and (3) continues to expand its service delivery to the international research community. Initially created to meet the increasing demands for an international consortium a decade ago, P^{3}G has since allowed international biobanks to oversee the technical, organizational and infrastructural aspects of their research with confidence that the tools used to build them have been the product of collaboration and leadership in the field.

Keywords Networking • Biobank • P^{3}G • Population health • Genomics • Policy • Data access • Harmonization

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1 Introduction

Biobanking represents an "ontologically distinct approach" [1] to generating scientific knowledge. As such, methods for collapsing the disciplinary silos that preclude collaborative engagement in the data-intensive sciences must be innovative and distinct if they are to serve the biobanking community effectively. Substantiating an imperative of collaborative science in population genomics, P^{3}G facilitates the building of empirical foundations in understanding human disease, creates a repository of publicly accessible tools and information and fosters interoperability among researchers and studies in population genomics worldwide [2].

Since its inception, networking has been a central focus in all P^{3}G initiatives. The creation of the P^{3}G consortium addressed the need for a formal international infrastructure to optimize design, construction, and maintenance of biobanks, while promoting necessary harmonization in policies and practices. Derived from the Latin word *consors* meaning "partner," a consortium seeks to associate individual groups or entities for engagement in a joint venture. Indeed, the P^{3}G mission to "promote the common good" (Charter of Principles, [3]) reflects this ethos of partnership. It makes networking the joint venture whereby public goods are generated vis-à-vis international collaboration for biobank research. P^{3}G's networking aims and philosophy of cooperation therefore exemplified the consortium approach to research at a time when the international research community struggled under the financial and institutional pressures of establishing biobanks.

With the goal of optimizing the time and resources of emerging biobanks, scientists expressed a desire to collaborate on persistent issues in studying population genomics. These included, data harmonization [4], data sharing and linkage [5] and ethico-legal policies governing participant privacy and data access [6]. It became apparent that the key to addressing these prevailing issues required an active international organization built around collaboration. Organized as a consortium, P^{3}G collaborators were better able to identify ethico-legal issues concerning international biobank practices, and ensured its tools provided the flexibility to tailor proposed guidelines to local specificities.

P^{3}G was therefore constructed in a modular fashion so as to be inclusive and easily adapted to evolving scientific, ethical, legal and economic climates. P^{3}G envisaged its own development as not only encouraging new collaborations, but to also aid its members and partners in developing their own platforms for data sharing and scientific engagement.

2 Phase I (2004–2011): Building Infrastructures

Phase I of P^{3}G's development and implementation prioritized facilitating interoperability and providing expertise to large population cohorts. P^{3}G collaborators identified seven key objectives:

- to educate, inform and increase awareness about the common challenges raised by population-based research and the important contribution of these types of research, so as to foster a positive research environment;
- to convince and obtain the support of population-based researchers and stakeholders to create a network with a clear focal point for international exchange;
- to generate cohesion, collaboration and synergy amongst partners so as to share knowledge, tools and research strategies amongst members;
- to increase the value, quality and coordinate financial support for large scale population studies;
- to coordinate with other international organizations with complementary missions;
- to facilitate access and sharing of tools generated by the consortium by putting them in the public domain;
- to support the research community in improving the health of populations.

These objectives underpinned the ways in which early P³G members sought to enhance networking capabilities and endeavoured to embed ethical and "legal norms into the technological infrastructures" [7] of international biobanks. Five International Working Groups (IWG) were thus established, each tasked with further investigating and proposing methods of action to address early issues such as:

- Socio-demographic health questionnaires;
- Physical/physiological/biochemical measurements, storage;
- Logistics and security;
- Governance and ethical clearance
- Public engagement

The IWGs capitalized on the new network structure, which effectively pooled knowledge and collective experience among P³G's growing consortium. Since the *raison d'être* of establishing P³G was to create a first-class research environment, it sought to organize and provide access to infrastructural tools that would support greater collaboration among biobank researchers. As opposed to executing the research protocols themselves, P³G collaborators underscored the need to advance "Core Projects." Supported by a firm networking foundation, these projects became the key scientific work units of P³G.

2.1 Networking to Build Epidemiological Tools

There were a number of significant advantages to designating a proposed research project as a P³G Core. Organized in this way, the Cores were allowed accessibility to scientific input from international researchers, swift dissemination of results to a wide community of colleagues through meetings, and direct support to scientists submitting grant proposals to various institutional funding agencies for new Core Projects. The restructuring of the Core Projects and organization of the IWGs

embodied the first phase of P³G's network building. As a result, the creation of the Observatory Catalogues and Repository of Documents and Tools—since renamed the P³G Catalogues and Toolkit—was heralded as one of the first major achievements of P³G [8]. Born from close collaboration on the aforementioned issues between members and affiliates of the IWGs, the P³G Toolkit now serves as an information dissemination module, support toolbox and data-sharing platform. In its inaugural years, the Toolkit provided a useful model to advance the organization of future disease-specific biobanks [9] and has since facilitated questionnaire design for other international biobank protocols [10–11]. Moreover, it was first to draw attention to regional biobanking challenges in an international forum. For example, the networking collaborations that produced the Toolkit highlighted disparities in biobanking resources between developed and developing nations. In response, its publicly accessible tools sought to narrow this divide [12].

P³G continued to target areas where it could concentrate international expertise. In recognizing the immense resource burden associated with large-scale population studies, P³G focused its efforts on alleviating some of these challenges through effective harmonization. According to Fortier et al. [13], an effective harmonization tool demands unique expertise:

> Given the quantity and complexity of the information generally collected by individual established studies and the heterogeneity of their designs and procedures, it is essential to have access to effective methods and tools to formally explore the potential to generate high-quality synthesized databases. Such tools need to provide comprehensive information on: (i) the specific variables that could be shared; (ii) the studies that could participate in targeted analysis; and (iii) the factors that could influence the potential to integrate information [13].

Together with partners from within the P³G network, the DataSchema and Harmonization Platforms for Epidemiological Research (DataSHaPER, [14]) were created as a scientific approach to facilitate data harmonization and ensure rigor in documenting the harmonization process at each phase of the biobank lifespan. First, DataSchema identifies a thematic set of core variables most relevant to the specific scientific context in order to facilitate data sharing between existing and future studies. Hence it can be "developed to provide a template for the prospective harmonization of emerging biobanks" (DataSHaPER). Each DataSchema can then be "partnered by corresponding Harmonization Units that provide a foundation for harmonizing studies relative to that particular schema". Figure 1 shows as example of how the DataSHaPER portal provide access to harmonized information pertaining to all phases of biobank lifepan [14].

2.2 Networking to Build Policy Tools

The immense diversity of biobank organization, data storage platforms, and sample collections [15] signals how biobanks have evolved to meet the needs of researchers and institutions [16–18]. The ubiquity of biobank-facilitated research is now well

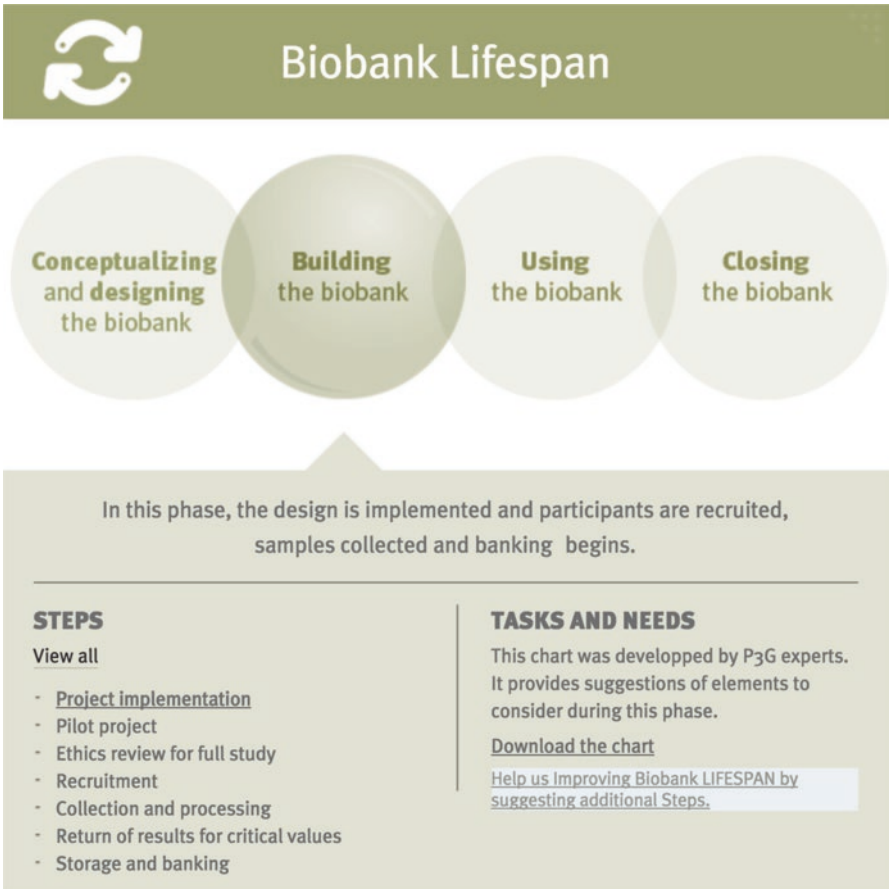

Fig. 1 Supporting biobanking harmonization through DataShaper

recognized and as Scott, Caulfield, Borgelt, and Illes confirm, "biobanks exist on every continent, even Antarctica" [19]. Though conducive to building a new research discipline [20], the variability of biobanks and their infrastructures raise considerable challenges [21–23]. In 2007, P³G members agreed an initial step towards meeting these challenges was to collaborate on a Charter of Fundamental Principles and policy tools—including the P³G Sample and Data Access Agreement, Model Consent Form, Return of Results policy and others—that would reflected P³G's commitment to attaining the highest standards of ethical comportment and research integrity:

- *Promotion of the common good*—P³G will optimise the benefits of collaborative research for the benefit of all.
- *Responsibility*—Protection of the interests of all affected stakeholders including families, groups, populations, researchers and research sponsors is the highest

priority. Every effort will be made to respond to the concerns of stakeholders in a timely and appropriate manner.
- *Mutual respect*—The development and sustainability of P^{3}G is based on responsibility, collaboration, co-operation, trust and mutual respect for others, which includes recognition of cultural diversity and the scientific specificity of the projects involved.
- *Accountability*—All standards, processes and procedures will be transparent and clear, developed on the basis of consensus, and aim to create best practice in the networking of population genomics resources.
- *Proportionality*—All research materials (such as data and samples) must be protected to the highest standards of privacy and propriety, while at the same time allowing and promoting the free exchange of ideas, datasharing and openness for the benefit of all.

Lastly, the degree of harmonization P^{3}G advocates not only encompasses the synthesis of data stored in collective databases [24, 25], but also the standardization of common terminology used to refer to biobank research, concepts and practices [26].

3 Phase II (2013–): Facilitate Access

Whereas Phase I concentrated efforts on building biobanks, Phase II focuses on the multidimensional facets of access and use. The first networking successes of Phase I inevitably shaped how P^{3}G would strengthen and expand its international network. Already well placed to see the communal issues researchers and biobanks routinely faced when building infrastructures, P^{3}G further tailored its networking strategies to meet the new challenges of "optimizing the use and access of biobanks and cohort studies, together with a new emphasis on integrating social science, administrative, and clinical data" [8]. As a direct result of its continued commitment to collaboration and networking beyond its initial objectives, P^{3}G now supports international biobanking in three meaningful ways.

3.1 Networking for Innovation

First, P^{3}G augments innovation in both biobanking practices and policy through creating spaces for purposeful networking. P^{3}G's meetings and workshops aggregate leading scientists and biobankers alike around priority areas that are deserving of special attention in the community. Additionally, P^{3}G's online forums called HUBs, provide a virtual platform for collaboration and shared discussion on policies and literature of interest. In past years, these meetings centered on issues such as harmonizing privacy laws to enable international biobank research [27],

bridging biobank research and health care [28], or introducing a safe harbor approach to challenges in translational genomics [29]. From P³G's meetings emerge areas for growth in research and development that incite subsequent efforts in biobanking innovation.

Perhaps most importantly, the meetings allow P³G members to exercise anticipatory and reflexive governance. That is, the purposeful networking vis-à-vis meetings encourage dialogue around proactive approaches to future issues or policy changes meant to address specific challenges real biobank communities face. According to Ozdemir, Faraj, & Knoppers [30] anticipatory governance is defined.

> As a new approach to manage the uncertainties embedded on an innovation trajectory with foresight, in order to devise governance instruments for collective "steering" of science and technology. As a contrast to hitherto narrowly framed "downstream impact assessments" for emerging technologies, [anticipatory governance] adopts a broader and interventionist approach that recognizes the social shaping of in- novation and technology design. [30]

In utilizing international networking platforms to practice anticipatory governance, P³G departs from a unidirectional flow of scientific knowledge and implementation typified in the data-intensive disciplines [31]. P³G's network capacities therefore encourage authentic coproduction and management of scientific discoveries in an ethically responsible and participatory fashion. It is true the use of public deliberation as a translational tool for biobanking innovation—and certainly for innovation in the incipient 'omics' disciplines as well—can seem untenable given the rapid development and maturation of biotechnology. Despite this, P³G collaborators propose innovative models for preserving engagement [32]. Concerted networking initiatives like those witnessed at P³G meetings, workshops and discussions using online HUBs thus ensure the democratization of scientific progress and accountability for the science it helps to create.

3.2 Networking to Improve Accessibility

Changes to the funding architecture of biobank research now names data sharing as a requisite component of sound scientific design. In turn, these requirements crystallize the importance of international collaboration in achieving sufficient data-sharing capability [33]. Kaye et al. report a number of areas where the impact of funding policies is particularly apparent. Among them is a new mechanism for oversight of data access, where "the question for many researchers has become *how* to share data, whereas previously it was *whether* the data should be shared at all" (authors' emphasis).

Empirical evidence suggests that incorporating multiple stakeholder interests in while maintaining ethical safeguards can grow exponentially complex [34], and tensions can arise when economic pressure to commercialize biobank research restricts the very open access approach the public sector espouses [35]. Indeed it is public trust in research efforts and perceptions of responsible distribution of public

resources that decline with commercial or industry association [36]. Of importance, therefore, is striking an ethical chord with the level of database governance for access [37].

Phase II also marked a transition in how P³G approached research for building new tools and capacities, and three independent and autonomous research programmes were organized in place of the WGs. This restructuring made clear the extent to which P³G was versatile enough to link together research bodies whose objectives were as numerous and varied as the P³G constituency itself. To date, P³G supports:

- The *Policy Research Programme*, based at McGill's Centre of Genomics and Policy (CGP), stands at the crossroads of legal, medical and public policy fields to promote prospective structuring and guidance for both research in genomic health sciences and its applications [5, 38].
- The *Maelstrom Research Programme* is an independent research programme aiming to optimize the use of study data and facilitate collaboration amongst networks or consortia of studies [13, 25].
- Finally, the *ELSI 2.0 Collaboratory* aims to catalyze an international "collaboratory" at the intersection of genomics, ethics, science and policy to make global research on ELSI (ethical, legal and societal issues) more effective, efficient, and economical [39, 40].

P³G enables the activities of these highly specialized, affiliated research programmes by providing administrative support and fostering close collaboration between each. Furthermore, these programmes are reflective of the multiple domains of expertise the consortium now encompasses within the biobanking enterprise. More than ever, population cohorts initiating new collaborations can benefit from the networking experience of P³G that helps them tailor the many communication tools to their specific needs (P³G website, mass mailing activities, social media, etc.) and disseminate their research findings for translational purposes.

3.3 Networking to Offer ELSI Services

Launched in September 2013, the International Policy interoperability and data Access Clearinghouse (IPAC) provides ELSI services to assist international researchers in meeting ethical and regulatory requirements governing genetic/genomic research in their home countries [41]. P³G-IPAC team members include international ethical, legal and social experts in the fields of biomedical research, biobanks, regenerative medicine, gene therapies, cancer, pediatrics, pharmacogenomics, rare diseases, and bioethics/law. These services are critical for multi-site research typical in the 'omics' disciplines i.e. genomics, bioinformatics, proteomics, pharmacogenomics etc.

At its core, P³G-IPAC assists researchers in overcoming the hurdles of legal and research ethics compliance by customizing necessary policies and documents and

preparing the necessary procedural tools according to specific research activities and jurisdictional regulations, both locally, nationally and internationally.

Since its launch, P3G-IPAC has been a strategic resource providing ELSI services and tools for more than 20 Canadian and international research collaborations. To date, P3G-IPAC boasts a number of major service accomplishments to the scientific community. The services offered under the P3G-IPAC are regrouped into three categories, namely ELSI Interoperability, Data Access Compliance Office (DACO) and the DataTrust.

3.3.1 ELSI Interoperability

The ELSI Interoperability service focuses on the development of project-specific ELSI documents, policies and procedures for prospective and retrospective research projects. With this service, P3G develops customized documents such as consent forms, patient information leaflets, recruitment strategies, notification and/or opt out mechanisms, and other similar notions. In addition, core policies surrounding access and data sharing, re-contact, return of results, publication and intellectual property are also developed. Other additional important documents such as material transfer agreements (MTA) or data transfer agreements (DTA), codes of ethics/conduct and specialized communications (e.g. vulnerable, deceased, pediatric, incompetent adults) can be prepared. Finally, P3G-IPAC can also evaluate ELSI interoperability of cohorts, namely the capacity of different resources (cohorts, biobanks, studies, etc.) to work with each other from a legal and ethical standpoint; develop e-consent templates; and support ethics committee submissions, including those for multi-site projects.

3.3.2 Data Access and Compliance Office

P3G-IPAC also provides project-customized Data Access and Compliance Office (DACO) services. This includes the reception and review of data access applications for access to controlled datasets, in conformity with the goals and policies of the project. In order to set-up the DACO, P3G-IPAC assists in the preparation of materials and forms necessary for the application process and can also provide guidance for cohort web pages. Once the initial access structure is in place, P3G-IPAC receives access requests addressed to the project and maintains an up-to date file for each request. Furthermore, via P3G-IPAC, a Data Access Committee is set-up to ensure a timely review of the access application, by a committee of experts, independent from the project itself.

3.3.3 Return of Results in Translational Research and the P^{3}G DataTrust

Due to concerns surrounding the return of clinically significant results to research participants in the context of translational projects [42], the P^{3}G-IPAC has developped a comprehensive return of results framework to enable the implementation of the DataTrust, a service aiming to address the concerns surrounding the secure return of clinically significant results in the context of personalized medicine research. The return of results framework innovates by including a variety of multidisciplinary actors in the process (clinicians, researchers, specialists in genetics, IT professionals, etc.), as well as the P^{3}G DataTrust which acts as a trusted third party to bridge the research and the clinical settings by performing an ethical due-diligence assessment and authorizing the project's key holder to re-link coded research results to associated participant ID (code), where appropriate. As part of this process, in addition to its role as the DataTrust, P^{3}G-IPAC can assist in the preparation of the documents to manage the re-contact and return of results (RoR) processes to delineate the roles and responsibilities of the stakeholders involved (including expert committees, development of specific aspects of the research protocol, return of results workflow and procedures).

4 Conclusion

P^{3}G provides the international biobanking community with policy tools and services to facilitate the technical, organizational and infrastructural aspects of research, with confidence that these tools are the product of collaborations with leaders in the field. Through interactions with these leading organizations, P^{3}G sophisticates traditional networking standards by creating a network of networks. Fundamental to the P^{3}G mission is to bridge international researchers and biobanks, which culminated in greater opportunities for innovation, wider accessibility to data and ELSI resources, and support for the harmonization goals of the biobank community at large.

P^{3}G continues to realize the vision, mission and voice of international biobank actors through facilitating the exchange of information and data, and keeps true to its mandate of fostering knowledge coproduction, transfer and translation. The evolution of public health and personalized medicine research depends on the cooperative alliance(s) of international researchers, a step first made possible by expanding the knowledge and expertise of the P^{3}G network.

In most, if not all business settings, networking is seen as a key investment from which stakeholder interests can be met, and a number of new opportunities may eventually arise. One can imagine a potential scenario holds true for the biobank community. Return on investment need not necessarily be measured in financial terms. The success of P^{3}G's network initiatives serves as the empirical capital with which scientific progress through collaboration in international biobanking can be made rich.

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Biobanks in Low Resource Contexts

Rita T. Lawlor

Abstract A rise is expected in non-communicable disease burden in low and middle income countries (LMICs) in the next 20 years. Stratified medicine and target therapies promise to ensure response to drugs and exclude adverse effects, but the genetic background of populations from LMICs is rarely addressed.

Biobanks are the currency for representation of LMICs' populations in scientific research. They can provide populations in these regions with the equitable opportunity for research to include their particular genetic and environmental make-up and provide solutions that are also applicable to them.

Lack of foundation healthcare services, aligned with the need for biobank infrastructure to be compatible with local conditions and conservation methods, affect the development of biobanks. Underlying this is the insufficiency of medical personnel expertise, trained technicians and researchers to provide diagnostic data annotation, to execute basic biobanking services and biobanking research. New technologies and increased annotation will permit harmonization of these biobanks.

Inconsistent regulations and ethical guidelines including cultural and religious limitations for acquiring samples/information and low prioritization or lack of understanding of the importance of biobanking in a public health context by government officials and policymakers impede benefit sharing and sustainability.

New models for ethical governance will address cultural and social structures that exist in LMICs and provide benefit sharing for biobankers, researchers and contributing populations. Research collaborations can facilitate economic investment, training, collaboration, publications, technology transfer, and health care improvements. Together with institutional investment to sustain permanent technical and scientific personnel, they can provide sustainability.

Keywords Biobank • Low income countries • Cancer • Research infrastructure • Personalized medicine • Genomics • Sustainability • Ethics • Governance • Pathology

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1 Introduction

The United Nations General Assembly has only met twice in its history to discuss a health issue. In 2011 it gathered to discuss the growing global burden of non-communicable disease. Low and Middle Income Countries (LMICs) are increasingly burdened by chronic non-communicable diseases. Indeed, the incidence of cancer is set to increase dramatically over the next 20 years, and four of five deaths due to chronic disease occur in low-income countries. These countries are inadequately prepared to meet this impending public health challenge. 90% of economic resources earmarked for research are dedicated to addressing diseases occurring in developed countries, representing only 10% of the global burden of disease. This includes research on diseases occurring globally but without considering the underlying ethic, genetic and environmental implications that affect those in low-income contexts [1]. This infers the potential ineffectiveness of drugs developed from the use of biological material from populations in developed countries for populations in low-income countries.

2 The State of Cancer

The World Health Organization (WHO) projects that over the next 10–15 years, Africa will experience one of the largest increases in incidence and deaths due to cancer, compared to other regions of the world. An estimated 681,000 new cancer cases and 512,000 cancer deaths occurred in 2008, and these figures are projected to increase to over one million cancer cases and one million deaths by the end of the decade. The continent of Africa comprises 29 of the 43 low income countries (Table 1). Africa's current and projected cancer burden is attributed to multiple factors including increase in life expectancy [2]. Attention and resources to combat HIV/AIDS, tuberculosis, malaria and other infectious diseases have played a pivotal role in contributing to this increase in life expectancy. Additional drivers which are increasing the cancer burden are HIV, urbanization and changes in lifestyle associated with economic development affecting diet, lack of physical activity, change in reproductive patterns, increased alcohol and tobacco use and other occupational exposures associated with agricultural or industrial development [3].

As in other LMICs, the mortality rate in Africa is high compared to the rest of the world. Indeed the estimated age-standardized cancer mortality rate is 77% for Africa while in developed countries this percentage stands at 40% [4]. This cancer burden in Africa is further exacerbated by the low survival rate following diagnosis due to advanced stage at diagnosis and limited treatment options. Even when health services are available, cultural norms in many countries of sub-Saharan Africa do not permit surgical intervention at advanced stages of disease. This reduces the possibility to collect these cancer specimens for research.

Table 1 Lower and lower middle income countries

Low income countries					
Afghanistan	Bangladesh	*Benin*	*Burkina Faso*	*Burundi*	Cambodia
Central African Republic	*Chad*	*Comoros*	*Congo, Dem. Rep*	*Eritrea*	*Ethiopia*
Gambia, The	*Ghana*	*Guinea*	*Guinea-Bissau*	Haiti	*Kenya*
Korea, Dem Rep.	Kyrgyz Republic	Lao PDR	Liberia	*Madagascar*	*Malawi*
Mali	*Mauritania*	*Mozambique*	Myanmar	Nepal	*Niger*
Rwanda	*Senegal*	*Sierra Leone*	*Somalia*	Tajikistan	*Tanzania*
Togo	*Uganda*	Uzbekistan	Vietnam	Yemen, Rep.	*Zambia*
Zimbabwe					
Lower middle income countries					
Albania	Angola	Armenia	Azerbaijan	Belize	Bhutan
Bolivia	*Cameroon*	*Cabot Verde*	China	*Congo, Rep.*	*Côte d'Ivoire*
Djibouti	Ecuador	Egypt, Arab Rep.	El Salvador	Georgia	Guatemala
Guyana	Honduras	India	Indonesia	Iran, Islamic Rep.	Iraq
Jordan	Kiribati	Kosovo	*Lesotho*	Maldives	Marshall Islands
Micronesia, Fed. Sets.	Moldova	Mongolia	*Morocco*	Nicaragua	*Nigeria*
Pakistan	Papua New Guinea	Paraguay	Philippines	Samoa	São Tomé and Principe
Solomon Islands	Sri Lanka	*Sudan*	*Swaziland*	Syrian Arab Republic	Thailand
Timor-Leste	Tonga	*Tunisia*	Turkmenistan	Ukraine	Vanuatu
West Bank and Gaza					

The World Bank country classification by income (http://econ.worldbank.org/WBSITE/EXTERNAL/DATASTATISTICS/0,contentMDK:20421402~menuPK:64133156~pagePK:64133150~piPK:64133175~theSitePK:23941900.html#Low_income, accessed July 4, 2016). Countries indicated in *italics* are African countries. 29 of the 43 low income countries are part of the continent of Africa while 11 of the 55 lower middle income countries are African countries

The World Health Organization has outlined the need for evidence-based programs of prevention, early diagnosis, treatment and palliative care, which are difficult to achieve in the absence of biological material on which to develop hypotheses for these programs.

3 The State of Research in Low Resource Contexts

Limited resources conducive for research coupled with inadequate funding hamper research in low resource countries. The challenge for most countries is how to expand health services to meet growing needs with limited resources. A study reported in the World Health Report 2013: Research for Universal Health Coverage [5] qualitatively assessed health systems research in 26 LMICs in Africa, Asia and South America. The report identified that in order to provide universal health coverage (access to quality health services without risking financial hardship), a strong, efficient, well-run health system; access to essential medicines and technologies; and sufficient, motivated health workers are required. The study concluded that low-income countries carried out less health systems research than middle-income countries. LMICs have very little research capacity, with some exceptions such as Ghana and India [6].

There is a need for a change in priorities of research investment to strengthen research capacity and develop tumor biobanks in low-income countries in order to address the inequity that exists in international research. Research training programs are limited or nonexistent in most countries. Middle-income countries have greater numbers of researchers and a more diverse disciplinary mix than low-income countries. In many parts of sub Saharan Africa research training is inadequate and requires policy makers to rely on external research efforts. Therefore, research in low-income countries tends to be driven by donors, international agencies or international consortia. The positive trend is that interest in health systems research has been growing steadily in more than half of the countries surveyed [5]. One example is the Academic Model for Providing Access to Health care (AMPTH; http://www.ampathkenya.org/) set up in 1997 by a group of North American academic institutions to partner with Moi teaching and referral hospital in Edoret, Kenya (http://www.mtrh.or.ke/) to provide clinical support, improved education and training and introduce trainees to research methods.

4 The Need for Biobanks in Low Resource Contexts

Current knowledge dictates that cancers are insufficiently defined by their organ of origin, rather they are as different as the people affected by them. They are defined by inherited genomic variation and somatic genetic events [7]. Information regarding genetic alterations show that tumors of the same organ can be split into prognostic and therapeutic subgroups based on molecular alterations. This means that even the most frequent cancer type is comprised of many subtypes, making each subtype more rare. This molecular diversity of tumors is compounded by genetic variability not only of the cancer but of the individual [8, 9]. This genetic and population based variability affects whether indeed a genetic variant is simply a population based

variant that does not result in the development of disease or a potential indicator of disease risk [10, 11]. Infectious diseases such as malaria are also affected by this genetic variation where the disease is prone to genetic variability based on its geographical origin [12]. Africa is known to have a high human genetic variability [13], which affects risk, disease and treatment response [14]. Factors that may influence the etiology of cancers such as gastric cancer include the genetic diversity of the infecting helicobacter pylori strains, differences such as polymorphisms in pro-inflammatory cytokines in the genetic makeup of the ethnic group to which the patient pertains, in addition to diet, hygiene and environment [15]. It has been shown that population based molecular variation of individual and the disease cause differences in treatment outcome following drug therapies for a number of cancers such as lung, breast, colorectal, and stomach cancer [16]. Unfortunately, many of the studies performed to address ethnic diversity have taken place in countries where second or third generation immigrants make up the ethnic sub-populations and therefore are not entirely representative of the original population that hails from LMICs. Furthermore these geographically displaced populations tend to be grouped into a larger continental group and therefore the true population based genetic diversity may be masked.

Biological banks pave the way for larger collaborative research that can provide the answers for global public health issues [17]. By effectively coordinating the collection and use of samples in a standardized and organized manner, it is more likely that research will produce more effective results that, in turn, can be validated on larger sets of non-biased samples and correlated with harmonized sets of data to generate clinical applications for the benefit of the health care system. Without the availability of biological materials for research from low-income countries, the advances made in the era of genomic studies and personalized medicine to stratify diagnosis and therapy of diseases such as cancer will not necessarily be applicable to individuals affected by these diseases in low-income contexts.

Biobanks are the currency for representation of populations in low-income countries in scientific research. The ability to contribute to the large statistically relevant study numbers required to address disease and ethnic genetic variations will attract more collaboration from developed countries. Biobanks can act as drivers for investment, not only in economic terms to increase the collection of the biological materials, but also in terms of knowledge and technology transfer to effect more advanced research [18]. They can provide populations in these regions with the equitable opportunity for research to include their particular genetic and environmental make-up and provide solutions that are also applicable to them [19]. The importance of biobanking on health research advancement in LMICs can be seen by the impact the tumor bank at the A C Camargo Hospital, a cancer care and research center located in Sao Paulo, Brazil had on research and knowledge of prominent cancers in the region (Box 1) [20]. Another example of this impact that biobanks have on research and public health in LIMCs can be seen in the Malaysian Oral Cancer Database and Tissue Bank System (MOCDTBS) (Box 2) [21].

Box 1 The A C Camargo Hospital Tumor Bank (ACCHTB)
Established in 1997 to provide human tissue samples for the Human Cancer Genome Project, an initiative by the Sao Paulo Research Foundation (FAPESP) and the Ludwig Institute for Cancer Research.

Following patient consent, tumor tissue is collection by pathologists in the frozen section room after surgical excision. Sample selection, registration, and freezing take place within a 30 min window. A blood sample is also obtained and processed in order to obtain and preserve plasma and genomic DNA from leukocytes. 36,000 samples (fresh frozen tissue, FFPE tissue, whole blood and derivatives, DNA and RNA) have been collected from approximately 15,000 patients. Analysis of impact of biobanking in the overall quality of research projects performed showed: (1) increase in the number of international publications; (2) increase in the impact factor of the publications; (3) increase in quality of doctoral and post-doctoral medical research.

Box 2 Malaysian Oral Cancer Database and Tissue Bank System (MOCDTBS)
Established in 2006 through partnership of University of Malaya (UM) spearheading this effort. Other partners in the partnership include six major Ministry of Health (MOH) referral hospitals throughout the country, Cancer Research Initiatives Foundation (CARIF) and Universiti Sains Malaysia (USM).

Increasing efforts have been made worldwide to study the underlying mechanism of cancer and its association with genetic, environmental and lifestyle factors. In Malaysia oral cancer is not as common as breast or prostate cancer, however it is one of the most common causes of death due to cancers. This MOCDTBS novel approach permits the acquisition of an extensive range of genetically varied biological specimens from various ethnic groups in Malaysia. Analysis of Pubmed revealed that the number of publications have increased by 57.6% within the last decade where 39% of research reports were produced utilizing resources from the MOCDTBS.

5 Collaboration Between Biobanks and Industry: Pharma

Biobanks in low resource contexts should address the collection of biological materials and data to fuel medical research that contributes to the global research understanding, but should also pay particular attention to locally relevant research.

More importantly, the creation of a biobank provides the opportunity for pharmaceutical companies and industry providing companion diagnostics to validate their products on larger and more heterogeneous numbers. This has the double bonus of attracting industry investment but also validating the ability of drugs to work on ethnically and genetically diverse groups and assist in the tailoring of these drugs to those who can benefit from them. One example of targeting drugs to specific populations is the study carried out in the US for the drug BiDil [22] that was rejected by the FDA because its efficacy could not be demonstrated statistically in a US nationwide clinical trial, but was endorsed after impressive results on an exclusive group of African American patients.

The arrival of stratified medicine and the need to evaluate the heterogeneity of tumors and individuals to devise stratified therapies to target the tumor, to ensure a response to drug treatment, and to exclude adverse effects, requires that pharmaceutical companies perform clinical trials on groups selected based on genetic make-up (Fig. 1). This changes the model for evaluating and introducing drugs to the market, as it requires the selection of patients based on molecular classification of both the tumor and the individual before embarking on clinical trials. This is an opportunity for pharmaceutical companies to involve diverse populations in validation studies before being included in clinical trials [23]. Only 16 of the 1393 drugs marketed between 1975 and 1999 were for diseases that affect populations in LMICs. To date,

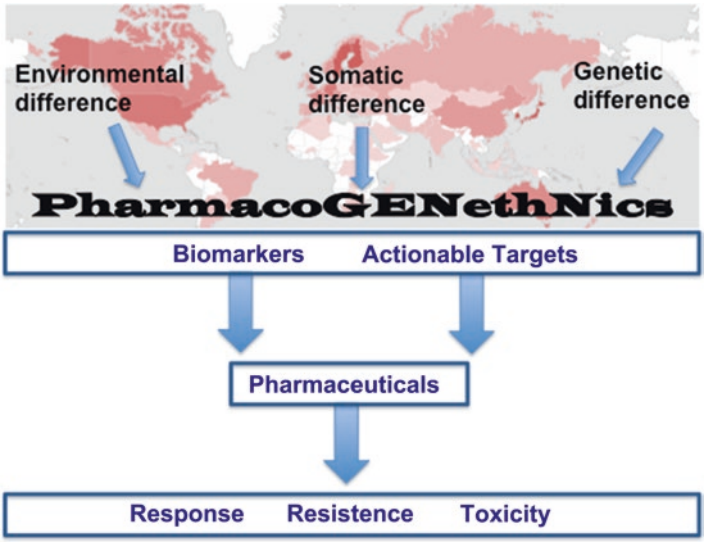

Fig. 1 Disease mutations may be due to alterations from the disease, from the gene of the individual or due to alterations caused by lifestyle and exposure. These alterations provide biomarkers that may be used to identify or classify more accurately the disease or may be targets for which therapies are available. The genetic makeup of the individual not only provides an indication of the likelihood of the pharmaceutical to function based on the match between drug and target but they are also potential indicators of alterations that provide resistance and risk of toxicity

populations from LMICs are only involved in 15% of clinical trials, and this number is twice that of the previous 5 years. Validating drugs on populations in developing countries would thus open a new market comprising 85% of the world's populations to pharmaceutical companies [24]. In order for this to happen biobanks of patient and donor samples representing the diverse ethnic genetic variations must be available for pre-clinical validation studies.

6 The Current Situation of Biobanks in Low Resource Contexts

Until recently, samples collected in low-income countries were study specific collections, many of which did not remain in the country but were sent abroad as part of the study. The shift in understanding of the requirement for an ethical and sustainable method of collecting samples in a homogeneous manner to ensure reliable and reproducible research has promoted the creation of a number of biobanks, which are now active in LMICs. Most biobanks have historically collected samples for HIV research. There are a few examples of such collections created as part of study specific grants that have grown into important research biobanks such as those in Kenya and the Gambia. The latter is a DNA bank established by the Medical Research Council for research on HIV/AIDS, Tuberculosis and Malaria (Box 3) [25]. Many additional biobanks have been created in the past 5 years with collections, ranging from 1000 to 100,000 samples. Some countries have aimed to create national biobanks, including the Gambian National DNA Biobank, the Mexico City Prospective Study and the Indian National Biobank. Others have attempted to unite independent hospital and laboratory based biobanks into a network structure such as the South Africa Biobank Network (SABN).

Box 3 The Gambian National DNA Bank

The national DNA bank in The Gambia, which was established in November 2000 by the Medical Research Council has a current repository of approximately 50,000 DNA samples and associated data. The DNA bank is a major infrastructure for health research and serves as a repository of human DNA samples. Its operations are regulated by the provisions of the Gambia Ethics Committee for sample collection, archiving, data storage and privacy protection and is recognised by the World Health Organisation as the first biobank in Africa. With the broad aim of supporting studies on the genetics of complex diseases, the DNA bank facilitates research to improve the prevention, diagnosis and treatment of a wide range of diseases but focusing primarily on malaria, HIV and tuberculosis. The program will also be developed to enable the collection of samples for use in future research.

Box 4 Integrated Biorepository of H3Africa—Uganda (IBRH3AU)
IBRH3AU is an integrated biorespository under the H3Africa Biorespository Initiative located at Makerere University College of Health Sciences (MakCHS) a Center of Academic Excellence, Health Care and Collaborative Research. MakCHS was historically established as an informal paramedical teaching center within Mulago National Referral & Teaching Hospital in the late 1890s and today conducts some of the most relevant and high-impact research in infectious and non-infectious diseases.

IBRH3AU provides a resource of well characterized and annotated quality biospecimens to be used by future studies. This resource is utilized by communicable and non-communicable disease researchers in an African population with the ultimate goal to improve the prevention, diagnosis, and treatment of illness and the promotion of health throughout society. Biological banking offers an opportunity to answer new questions or test old questions with new methods. Stored Biospecimens provide a unique opportunity to African scientists to study the genetic characteristics (http://www.ibru.mak.ac.ug/).

There has also been a particular drive to advance the study of genomics and environmental determinants of common diseases with the goal of improving the health of African populations by developing the necessary expertise among African scientists to establish networks of African investigators. This initiative, known as H3Africa (Human, Heredity and Health in Africa), is funded by the National Institute of Health (NIH) and the Wellcome Trust [26]. In addition to providing funding for specific research projects and collaborative centers, it has also granted funding for the creation of biorepositories. As of 2014, H3Africa had funded four requests to develop biorepositories, and these have completed the first feasibility phase. This phase is intended to build on existing infrastructure and develop plans for the creation of a full-scale biobank to be funded during the second phase. The biobanks created under this program are intended to provide an international site for the receipt, storage and distribution of samples from H3Africa research projects as well as other African genomic research studies [27]. One such example of this is the Integrated Biorepository of H3Africa—Uganda (IBRH3AU) established at the University of Makerere in Kampala, Uganda (Box 4).

7 Factors Affecting Biobanks in Low Resource Contexts

While the elements that comprise a biobank remain the same, regardless of the geographical and economic context in which they are created, the manner in which these elements are developed will be different to adequately address the diverse restrictions. Biobanks in LMICs face particular challenges [6].

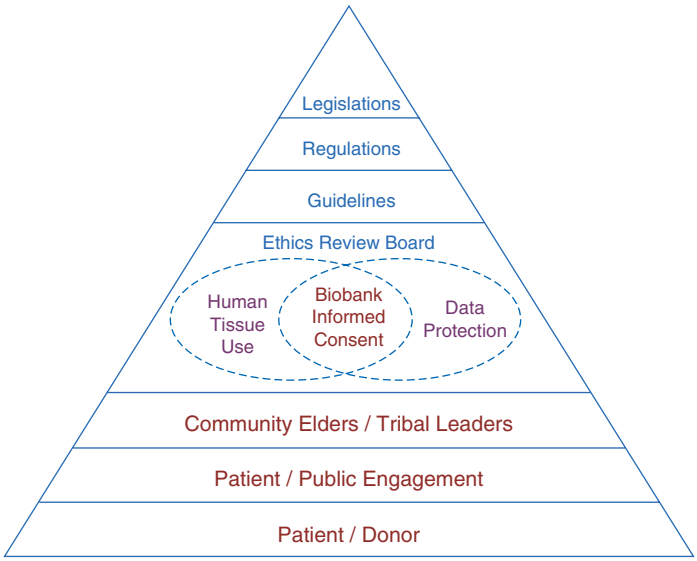

Fig. 2 A hierarchical representation of elements involved in the process of accessing biological material and data of an individual. The process circulates around the ethics committee or review board that evaluates the final document (informed consent) requesting permission from the individual in consideration of legislations, regulations and guidelines on human tissue use and in respect to protection of personal data. For LMICs that may have community-based interaction or for indigenous groups that may be considered vulnerable in a western context, intermediaries or representatives such as elders or leaders should be involved

Lack of foundation healthcare infrastructure and services, aligned with the need for biobank infrastructure to be compatible with local conditions and conservation methods, affect the development of the biobank and its ability to respond to specific research requirements. Underlying this is the insufficiency of medical personnel expertise, trained technicians and researchers to provide diagnostic data annotation, to execute the basic biobanking services and biobanking research. Lack of data registries providing accurate information on the state of disease in the geographical area of interest prohibits a complete analysis to identify the health areas for investigation. Inconsistent or absent regulations and ethical guidelines, to encompass cultural and religious limitations for acquiring donor samples/information and low prioritizing or lack of understanding of the importance of biobanking in a public health context by government officials and policymakers, impede benefit sharing and sustainability (Fig. 2).

8 Pathology Services

Cancer care is a multidisciplinary effort that revolves around the pathology diagnosis, which drives the clinical decision making process of treatment, prognosis and follow-up. The activities of assessing biopsies and excised diseased organs,

preparing frozen sections to review tumor margins, evaluating tumor type and composition, determining prognostic and predictive markers and performing immunophenotyping and molecular diagnostics are all part of the pathologist's role in cancer care [28]. This requires several steps: obtaining a representative sample, timely transportation, processing, evaluation, reporting, archiving, retrieval for review and analysis. These steps run in parallel to those required by a tumor biobank and underline the fundamental role pathologists play in tumor banking as part of the tissue sampling routine. The pathologist has a greater role during the process of accessing and preparing tissue samples for use in research. Cancer tissue is heterogeneous in nature and its composition changes through very small sections [29]. Thus tissue sectioning requires continual verification by the pathologist to confirm cell content. This is also necessary in the process of nucleic acid extraction from tissue, as it is important to verify what tissue has been extracted. The pathologist is also essential in the activities of micro dissection and Tissue Micro Array creation as only the pathologist can identify the areas of interest to be selected.

Lack of pathologists creates a fundamental problem, that of clinical diagnosis. Whereas in developed countries the problem relates exclusively to the non-standardization of ontology, in low resource contexts it is the diagnosis itself that may be lacking. This is due to the fact that there is less than one pathologist per 500,000 people in sub-Saharan Africa and in many countries less than one pathologist for every million people [30]. This number equates to, at best, 10% of that in higher income countries [31]. Poor pathology infrastructure undermines biobanking and consequently research initiatives. Development of in-country research programs can be used to guide public policy decisions, resource allocation and train future personnel. Addressing this requires the support not only of the medical and hospital administrative staff but also the ministries for health and research to create a sustainable integrated model of diagnosis, training and research by integrating the parallel processes of diagnostics and biobanking to improve pathology services and create the basis for research initiatives [32].

9 Cancer Registries

Cancer registries are a vital cancer surveillance program that monitors the state of incidence, mortality, treatment, progression and survival in a region or country. Cancer Registries are a wonderful way to identify patient cases and obtain basic information regarding the patient's disease. They also provide an excellent overview of the nature and evolution of cancer patterns on a local, regional, national and continental level. Unfortunately, cancer registries are not well established in LMICs. Cancer Incidence in Five Continents, vol. IX [33], showed that registries covered only 6% of the population in Central and South America, 4% in Asia and only 1% in Africa. This 1% represents the five cancer registries that were considered to have data of sufficient quality to be included, while another 42 registries covering an additional 5% of the population of Africa were not included due to lack of quality.

The issues facing cancer registries are very similar to those that face a tumor research biobank: immature health care infrastructure, insufficient financial resources, lack of trained personnel, poor communications, unreliable data, cultural and religious limitations and low prioritizing of the requirement by government officials and policymakers. This is perhaps due to lack of understanding of the need and the value of this surveillance system as an integral part to clinical care and identification of relevant research programs. The factors that have led to the success of cancer registries will consequently be similar to those that constitute a successful biobank: start-up and medium term running costs, support from officials and trained personnel, quality of data collected and follow-up information. One demonstration of this is the East African Cancer Registry Network [34] that received initial funding from the Doris Duke Charitable Foundation. This has been successful enough to attract funding from GlaxoSmithKline (GSK) to expand their activities into The African Cancer Registry Network (AFCRN) [35].

Nevertheless, the number of cancer registries remains insufficient and the quality of existing registries is lacking in terms of completeness and data validity. The International Network for Cancer Treatment and Research (INTCR) cancer registry program and International Agency for Research on Cancer (IARC) Global Initiative for Cancer Registration are working to improve existing registries, establish new ones and stimulate regional hubs. These networks can provide a source of information for tumor biobanks in these countries. This information is vital for translational and applied research that uses the biobanks' samples to validate and stratify the sample derived research data. The importance of biobanking and linkage to cancer registries as a research platform and as a monitor of cancer incidence is demonstrated in the Gambia Hepatitis Intervention study (GHIS) [36, 37].

10 Ethical, Legal and Social Issues

Ethics and science are not separable and biobanking is the discipline that perhaps most perfectly defines this as it arbitrates the use of human derived biological materials in scientific research. While there are universal principles of ethics, in low-income countries all ethical issues regarding the collection and use of biological human materials and personal information must respect local ethical standards and must take language, culture and regulatory structures into consideration. The World Medical Association Declaration of Helsinki [38] regarding Ethical Principles for Medical Research Involving Human Subjects specifies the provisions for use of human samples. While it does not specifically refer to biobanking, it is intended as a gold standard for the ethical acquisition and use of samples for scientific research.

The issue with regard to ethics is based on the underlying concept of ethics and how it is interpreted in the context of research and the researched. Ethics, the rules of correct and moral behavior, are intimately related to the individual understanding of selfhood, to the values of life held, to the individual's relationship to the community, and universe and the understanding of the purpose and meaning of life [39].

Ethics are integral to the way of life of a people and imposition of rules derived from other ways of life will inevitably cause problems. Success can only be found through common understanding and shared interest.

The interpretation of similar terms such as ethics, healing, self is part of the cultural context and takes on different significance, which must be part of any ethical biobanking approach, particularly in LMICs that have genetically, culturally and geographically diverse populations. There are many unspoken assumptions that guide behavior in indigenous peoples where traditional teachings are conveyed through story telling to demonstrate examples. Aboriginal research has demonstrated how these issues of language and context require a specific bioethics [40]. In many tribal cultures in Africa the individual exists in reciprocal relationship with one another and life is only real if it is shared. Ubuntu, an ethical concept from Southern Africa is the epitomy of such communal philosophies [41]. This is in complete opposition to the more reductionist individualism of developed or western cultures and therefore must always be considered when attempting to apply western based ethics and notions for biobanking and research [42]. It is important, however, that there are no applications or assumptions based on stereotypes as indigenous populations may not be homogeneous and generalizations are inappropriate.

11 Regulations in Low and Middle Income Countries

Regulations applicable to the collection and use of human biological materials and donor data can be found dispersed in different declarations, such as acts governing the use of human tissue. Even in developed countries, specific regulations that govern the discipline of biobanking may not exist but are inferred in such declarations as the Human Tissue Act and Data Protection Regulation explicitly addressing the use of samples and data for scientific research. The International Compilation of Human Research Standards 2013 edition provides a snapshot of the situation regarding general research legislation and regulations and those for clinical trials, use of human material and data protection. A review of this edition demonstrates the lack of government legislations often in many LMICs although it should be noted that only 14 of the 54 African Union countries are listed [43]. Some countries have general acts such as Tanzania (National Institute for Medical Research Act), Uganda (National Council for Science and Technology), and Nigeria (National Health Bill) while other countries such as Kenya and Malawi have more specific regulations regarding Research and Development of HIV/AIDS Vaccines and Access and Collection of Genetic Resources respectively [44].

Many countries in Africa have regulatory bodies with guidelines for the use of biological samples for research, such as The Gambia, Rwanda, Zimbabwe, and Ethiopia [44]. The Department of Health in Kenya has published Guidelines for Ethical Conduct of Biomedical Research Involving Human Subjects in Kenya [45] and the National Health Research Ethics Committee of Nigeria has published a National Code of Health Research Ethics that addresses issues of use and distribution

of biological material for research. Brazil is one of the few countries to have legislation specifically addressing biobanks in an ordinance on *Establishing the National Guidelines for Biobanks of Human Biological Materials for Research Purposes* [46]. In the genomic era, regulations must address the modern requirements of access to molecular material and associated data to ensure that the donor's rights to privacy and protection are upheld. Some low-income countries have already addressed the concept of personal data with Personal Data (Protection) Bills such as that of India, where in its Bill of 2013 on Sensitive Personal Data, deoxyribonucleic acid data is expressly named [47]. It is defined in the Bill as all data, of whatever type, concerning the characteristics of a person that are inherited or acquired during early prenatal development. This definition paves the way for the possibility of using genomic data for research evaluation. The Bill does include provisions for the use of this data in research, with the application of sufficient controls. Where national guidelines do not exist, international guidelines such as those provided by OECD, IARC and ISBER can be used to address legal and ethical aspects concerning the collection and use of biological material and data for cancer research. However, traditional cultural values placed on human biological material by local communities must be taken into account.

12 Informed Consent in Low-Income Countries

Ethics considerations in developed countries has determined that the individual's right to self-determination and autonomy is the basis of ethical considerations, and implies that the individual must have the ability to choose whether to participate in providing biological material and personal data to a research biobank and the right to change their mind and withdraw at any time. This voluntary participation is a universal ethical principle, but attention to the individual is less universally applicable. Many countries in low-income contexts are based on community and tribal organizations and as such, all ethical considerations regarding the participation of the individual should include the approval by community and tribal leaders [48].

Informed consent is a fundamental legal and ethical principle in research biobanking. It underlines the basic rights of autonomy, liberty and dignity. It outlines the agreement between the donor and the custodian biobank on the provision of samples and data for research. Any deviation from this consent must be authorized by a supervisory board, such as an institutional ethics review board. Even in developed countries, it is valid to question whether consent for participation in a study or to donate biological specimens and information to a research biobank is ever really informed. There has been much discussion on the use of the term informed, particularly for those consents that are broad or requests for future unspecified use, and therefore cannot contain enough information on project details and potential results. Conversely, it would be unreasonable to assume that the general public can understand specific scientific detail and be consequently well-informed. In low resource countries where the basic systems of health and education are immature or

inaccessible to the majority of the population, the concept of consent that is informed is exacerbated. The premise of informed consent is that donors understand the nature and purpose of the request being made to them to conserve their samples and data for use in research. Therefore, the information contained in the explanatory portion of the request must be simple, clear, in the colloquial language of the donor and fitting to their circumstances. This has to include the ethics and world view of the individual as part of an ethic or indigenous group and the semantic translation of terms to the context of their belief system. In Madagascar, the Akbaraly Foundation launched the 4awoman project in 2010 to battle breast and gynecological cancer and raise awareness by sending trained volunteers to rural areas where the majority of population resides to speak with women in local dialect during their collective daily activities (www.fondationakbaraly.org, www.4awoman-madagascar.org). The Epidemiology of Burkitt lymphoma in East-African Children and Minors (EMBLEM) consortia has gone a step further and integrated their research within the healthcare system. As such, health communication messages have been created and community assistants have been trained as local point of contact for the community to direct patients to centers for diagnosis and treatment [49].

Regardless of context, the information provided must explain how donor identity and sensitive personnel information will be protected. The donor must be aware that they have the right to withdraw their samples/data and the procedures that will be followed in this event. The consent information must clearly indicate the intention to share samples and data with others nationally or internationally, whether commercial or institutional. This is especially important where national regulations do not address cross border sample sharing to control the historic usurpation of samples by international research. It is also important that the donor realizes the return on the donation, whether they can expect any benefit from the donation either monetary or follow-up health care [50]. In the past, these methods have been used to garner consent for samples and data, and may ethically be considered coercion, particularly in low resource countries where much of the population lives below the breadline. Here again, the potential for community or ethnic group involvement may facilitate the ethical benefit and provide a more just hierarchical format that gives true power to the consenter. Ethics guidelines define vulnerable subjects as those who cannot give their consent or may be easily coerced or influenced into giving their consent, and for which guardians are delegated to provide consent. In LMICs, the hierarchical format of community involvement for consent could be applied here too and thus the hierarchical consent model would be all-inclusive (Fig. 2).

13 Governance

At variance with traditional collections that tend to be project specific, biobanks collect material for future undetermined research use and this requires a governance structure (Fig. 3). Biobank governance must respect donors and guarantee respect, privacy and confidentiality. At the same time, the governance must not be

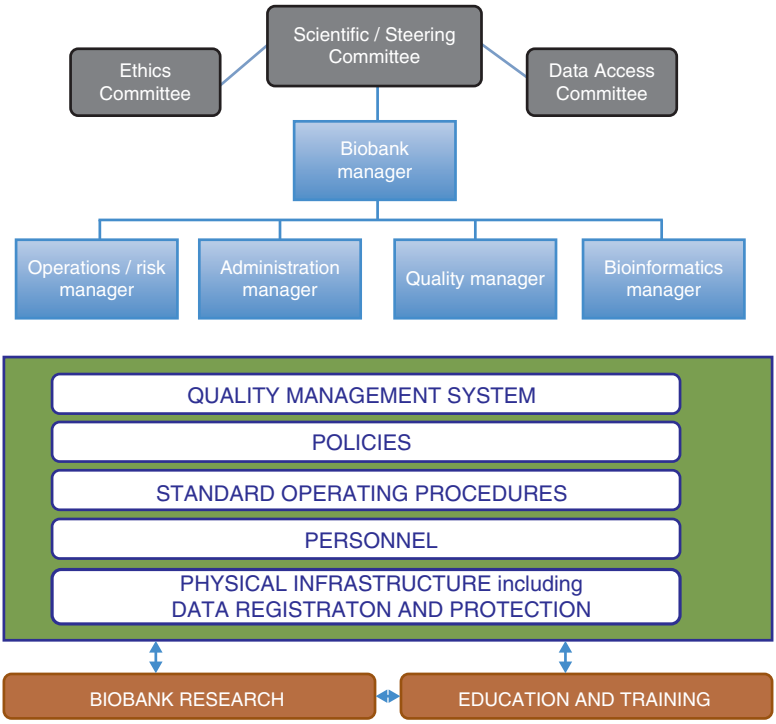

Fig. 3 A possible governance set-up for a biobank. In *grey*: the potentially external oversight committees that evaluate the ethical and scientific value of biobanking specific biological material and scientific projects that require material to be biobanked or to have access to biological material in the biobank. A data access committee is required when there is a need to evaluate requests to access data that may be considered sensitive and this includes research data that may have a moratorium imposed or may contain sensitive data. In *blue*: biobank managerial roles; in smaller biobanks multiple roles may be covered by a single individual. In *green*: the systems and procedures that govern biobank operations and the correct functioning of personnel and the physical biobank. In *brown*: the activities necessary to ensure the continued evolution of the biobank

so rigid concerning the provision of samples for potentially beneficial research. In low-income contexts where there may be no legislation or regulations governing the use of biological materials, it is important that a biobank have an established Governance entity to act as custodian in the equitable and ethical use of the samples provided by the individual or community and ensure a return for the biobank and the community [51].

A prominent ethical concern in research in Africa relates to ownership over samples and, to a lesser extent, data. Samples and their movement across borders seem to have become symbolic of concerns over exploitation and fairness and, therefore, have become stringently regulated in many African countries [52]. Data is however an issue that pervades biobanking research and pertains to the information that potentially affects not only the individual but a wider group, particularly in a community-based culture where knowledge belongs to the group and not the

individual. It can be likened to doing genetic studies on any individual where germline data is pertinent to the family and not only to the individual. The issue of germline data from research studies is currently being addressed in countries with advanced biobanking practices as it is a delicate issue relating to permissions for use of information that may affect more than the consenting individual and requires delicate handling. In LMICs where there is a large number of indigenous and community based groups and tribes, information that affects more than one individual goes beyond the idea of inherited familial information and as such data retrieved from any interaction with indigenous groups should be handled in an analogous delicate manner. It is important that individuals imparting information pertaining to the collective community has the community authorization to do so. The United Nations Educational, Scientific and Cultural Organization (UNESCO) [53] emphasizes the protection of human genome-derived genetic data [54]. The use of human biological resources and data for genetic research is addressed in the OECD Guidelines on human biobanks and genetic research databases [55].

14 Public Perspectives and Engagement

It is vital to assess public knowledge, attitude and willingness to participate in biobanking research, particularly with regard to issues indicated above and how biobank governance should respond to secondary use of samples and data over time and return of results. A study in Nigeria, carried out in 2012 [56] and conducted through focus groups discussions and key informant interviews with members of the general public in different regions, underlined the limited knowledge of the public regarding the discipline of biobanking and biobank research. The study demonstrated that, despite the historic prevalence of infectious diseases, the public were well informed on non-communicable disease and as such were willing to donate their specimens for this area of research. While they appreciated the need and utility of donating for future unspecified research, half of those interviewed wanted the right to re-consent (be asked each time their sample is to be used for research). This was perceived as a mechanism for continued communication with researchers to receive feedback. It also gave them a method to check that the use of the samples did not conflict with their religious convictions. Concerns focused on the issue of confidentiality for fear of discrimination and stigmatization. This concern extended to the use of the samples in international research where it was considered that there was a risk of discrimination linked to ethnic and national conditions. The study demonstrated that the members of the public interviewed considered that their government had a significant role in biobanking governance as they felt it would better safeguard national interests, particularly in an international context. The adaptation of the Community Engagement Research (CenR) framework [57] would augment community engagement in biobanking, thereby alleviating these concerns and enabling both the public and more specifically the patients. Through this engagement, patients would be involved in all phases of the biobank process from material and data collection to

evaluation of research requests [58]. This is never more true where the biobanking of samples and data is performed outside a clinical/patient context.

Indigenous cultures and communities, in particular, are complex and diverse with multiple political and cultural jurisdictions and it would be incorrect to consider applying a standard approach to community engagement when considering partnering with these groups for biobank and research purposes. It has also been suggested by Brunger and Wall [59] that the objective of involving the community on all research in service of standard ethics guidelines may cause more harm, by leading to community fatigue, undermining the community's ability to be effectively involved in the research, and restricting the community's ability to have oversight and control over research. Careful reflection on appropriate engagement for use of resources is required. Here the biobank may serve as the just intermediary along with elders within indigenous communities who have the credentials that are recognizable by the community and can translate into the language of the group the concepts of biobanking research, while at the same time reinforce the tribal world views to those outside of the community and involved in biobanking and research.

15 Benefit Sharing

Benefits for patients and those involved in the procurement of materials, such as clinical staff and local researchers, can range from recognition in publications, participation in collaborations, return of resulting research data, and health care improvements. However, historically this has not been the case. Terms such as *biotechnology gold rush*, *postal research, safari research* or *parachute research* have been coined to describe the methods used by foreign researchers exporting samples from low-income countries for research without providing benefit or collaboration locally [60]. A 2007 paper showed that 80% of all samples collected for research in Uganda have been exported [61]. A 2011 paper showed that DNA samples collected in Cameroon had been used in 96% of foreign publications, yet only 7% of these involved local institutes and 28% cited local authors [62]. Furthermore, the health issues investigated in these research projects regarded only 10% of issues that were of local relevance. As many foreign researchers never return to the country of collection, the local impact of the research findings is limited and tends to address issues of interest to the sponsoring country. This has promoted the notion of identifying LMICs only as sources of research material and created a feeling of suspicion and abuse within LMICs.

A lack of reciprocal collaboration and some form of return to the biobank are the most important challenges, but acknowledgment of the biobank and procedures to protect the donor are also considered important issues. Access to samples for research needs governance to ensure local benefit sharing. Procedures covering access to samples and data must be governed by ethics and access committees. Local governments must take responsibility for creating conventions to protect from potential abuse, by developing Materials Transfer Agreements (MTA) and

Institutional Review Boards (IRB). These committees should follow international principles and country leaders should restrict specimen exportation where no reciprocal benefit is envisioned. The focus should be on data sharing, solidarity and capacity building to guarantee an equitable return. The situation has improved with the investment in human capital in specific research collaborations and this form of reciprocal investment could be applied to biobanks and biobank research. A collaboration between the Ugandan Ministry of Health, University of Makerere and the University of Washington includes technology transfer in their patient-oriented research collaboration, and the involvement of biobanks could ensure that such a benefit is extended to the biobank. It has been recommended that direct patient benefits could include discounts on pharmaceuticals, but despite the enormous contribution of biobanks to clinical research, they are often too far removed from the application to be able to garner such benefits for the donating community [63].

16 Infrastructure in Low Resource Contexts

In LMICs, where funds to support health care infrastructure are lacking, dedicated biobanking facilities are not a priority. Initial development costs are thus a significant obstacle to establishing new biobanks. Even with the availability of financial resources to create dedicated biobank processing and storage facilities or integrate these facilities into already existing infrastructures, there are many challenges to operating a biobank in low resource contexts [64].

One issue that persists, perhaps due to the currently small potential market for suppliers, is the availability of follow-up onsite support and maintenance services for the equipment needed to run the biobank. This applies not only to storage equipment but also to processing equipment such as automatic nucleic acid extractors and histopathology slide scanners. Despite being standard equipment in hospital laboratories, many international suppliers do not offer local support services to supply technical maintenance in many LMICs, no doubt due to the small market incentive for suppliers. This underlines the shortcomings in health infrastructure. Maintenance is an issue that needs to be addressed up front and considered at the moment of planning the biobank infrastructure.

One of the many challenges for biobanks in low-income countries is the need to provide constant and consistent storage in order to ensure sample and data quality. The lack of regular utilities limits the possibility to constantly conserve frozen samples at −80 °C. Only dedicated generators to ensure real time back up of electricity can guarantee the quality of samples conserved in the frozen format. This may be an expensive alternative where the infrastructure of bio-bank facilities does not already provide for such back up.

The lack of a constant electricity supply can affect not only the operations of freezers. Computer based information systems used to both monitor the functioning of the biobank and to store the information on the biobank regarding sample tracking and the essential pre-analytical and clinical-pathological associated information

are also affected by the electricity supply. An irregular power supply will hamper any IT systems that are in place and will require control procedures to prevent power surges interfering with information processing and backups. Should monitoring systems lose power, the cascading effect of an unsupervised mechanical freezer biobank could be detrimental. This is easily resolved through the provision of a short term uninterruptible power supply (UPS) which is an inexpensive solution to a potentially disastrous problem. Information systems are an integral part of biobank infrastructure. The situation analysis carried out by IARC on biobanks infrastructure and facilities in LMICs [65] included a survey of the status of informatics software solutions for handling biobank sample registration data. The analysis indicated that most centers use basic and readily available software to register and track their biobank samples and data. The most common of these are Microsoft Access databases and Excel spreadsheet files. These approaches provide adequate possibilities for the registration of samples. They also provide basic search facilities to select sets of samples. They do not provide, however, the level of sample tracking and data auditing that biobanks in developed countries are required to have to respond to international standards. While there is an understanding of the need to have better developed systems to provide traceability for samples and changes to database information, it is not always feasible to purchase a standard off the shelf commercial product. The alternative is to attempt to develop an in-house system where informatics expertise is available, which can be a costly exercise. There is a move towards open source systems in an attempt to have IT systems without the need for substantial economic investment. This approach also requires the need for IT personnel dedicated to the biobank in order to be able to address the developing needs of the biobank. IT systems are also moving towards web based systems with the understanding that, for biobanks in these low resource contexts, it is essential that they have the means to be able to create easily accessible shared catalogues for the exchange of resources for research projects in their regions.

Environmental conditions in low resource contexts play a pivotal role in the creation and running of a biobank. Temperature and humidity influence the conditions of the biobank and require additional forethought in planning and monitoring of the facilities. Furthermore, biobank design in these contexts must consider what natural events are most likely to adversely affect the biobank in order to mitigate or avoid the potential risks. Natural risks, including earthquakes, hurricanes, floods and lightning storms, can not only cause direct damage to the biobank but can also have a cascading effect on service utilities and the correct functioning of mechanical storage systems. Therefore, low-income contexts necessitate that more complete disaster recovery procedures are in place for cold storage biobanks and IT systems.

Environmental conditions also affect transport services and the condition of fresh or processed samples collected at sites remote to the biobank. Bad transport infrastructure and potentially longer distances from collection site to biobank challenge sample quality. In consideration of these factors, new technologies are emerging which aim to address the issues of adverse conditions that limit transportation and conservation and provide practical solutions. Innovative examples look at the ability to transport and conserve blood samples and nucleic acids at room temperature.

Tumor biobanks tend to be integrated into facilities such as university hospital settings as they require the collection of tissue, and this can only be carried out in pathology labs in order not to interfere with the diagnostic routine. This implies that the quality of the material collected is necessarily linked to the quality of the clinical services provided, in particular pathology services. In low-income countries, these services may not be consistent with the standards of developed countries due to the lack of clinical facilities and personnel. While this provides access to a wealth of archival tissue, the conditions under which the tissue is sampled and processed are called into question. The quality of these samples is not immediately ascertainable due to a lack of standardization and pre-analytical information regarding the variable fixation times and unclear fixation agents. A basic approach for improving biobanking infrastructure in low resource settings should encompass the standardization of formalin fixed, paraffin-embedded (FFPE) tissue processing in pathology departments. High quality nucleic acids and adequate antigen preservation can be obtained from FFPE tissues. Alternative fixation agents have recently been developed that show advantages over current FFPE tissue processing techniques, inducing better integration of molecular characteristics, and may offer reasonable alternatives for robust tissue preservation. These tissue-processing techniques better suit the conditions in many low resource contexts, as they do not require extreme continuous temperature storage to maintain stability as long as integrity can be sustained during processing. However, it is important to realize that unless the developed world moves to these methods, doing so in LMICs would cause a lack of global standardization [66].

In the arena of tumor banks, it is also essential to have fresh tissue for the creation of cell cultures, human derived cell lines and tumor xenografts to increase the availability of biological materials. These techniques are normally only available in high technology, highly standardized infrastructures. Technologies such as those that provide the ability to maintain fresh tissue and cell viability at refrigerated temperatures for up to 96 hours, such as vacuum packing tissue specimens, provide limitless opportunities for biobanks to collect tissues from dispersed locations and provide centralized processing [67].

17 Personnel and Training

The infrastructure and quality of a biobank is intrinsically connected to the availability of trained personnel involved in the collection and processing of the biological samples and data. The biobank does not function in isolation; it is integrated into the healthcare system in some form and therefore is affected by the availability of healthcare personnel to complete the biobank processes that relate to the patient donor. Human resource challenges in low-income countries center on the lack of medical personnel and technicians to carry out biobanking services and to drive research-based biobanking. While dedicated biobanking training programs for technicians and biobanking researchers are still lacking, collaborative initiatives to train clinicians and researchers abound between developed and low-income countries.

Fellowships, such as the International Cancer Technology Transfer (ICRETT) of the Union for International Cancer Control (UICC), promote the professional development for health workers and facilitate the international transfer of research and clinical skills. An initiative between MD Anderson Cancer Center and the University of Ibadan aims to establish centers of excellence where specialists from pathology, gynecology, nursing and laboratory technicians can be trained in a virtuous cycle of research and healthcare where biobanking personnel play an integral role [68].

As previously stated, pathologists are the lynch-pin in tumor banking. Lack of pathologists for both clinical diagnosis and tissue retrieval prohibits the creation of a quality tumor biobank. The lack of on-site pathology personnel for diagnostics may be addressed with technological systems for tele-pathology to avail of tissue imaging and remote pathology expertise to provide diagnosis [69]. This can improve both the healthcare system for the patient and the accurate collection of research tissue. In addition to cooperative exchange programs for improved training and internships to provide temporary expertise in the field, another option is to alleviate the workload of the pathologist by training specialist technicians to perform certain activities in the pathology process. They can prepare diagnostic material as part of their role in preparing biobank samples [70] and learn to perform other tasks that the pathologist would normally have to do. Training non pathology medical and paramedical staff to perform simple diagnostic techniques such as fine needle aspirations or immunohistochemical assays, other diagnostic assays, training technicians in hematoxylin and eosin tissue section preparation, tissue fixation, all alleviate the burden on the pathologist and permit the integration of research biobanking into the diagnostic process.

As collections in low resource contexts will naturally be driven by research needs and sustained by research grants, it is important that the researcher be involved in the biobanking process and educated to the importance of this discipline as part of the research infrastructure. Underlying this is the capacity of researchers in low resource contexts to initiate research projects and this potential can be developed through collaborative programs with renowned international researchers. One such initiative for medical researchers is that between the University of Makerere and University of Washington. The initiative also includes as a formal partner the Ugandan Ministry of Health. The initiative is based on a 3 year PhD program to train research leaders, managers and implementers and includes clinical rotation, as these researchers will have to integrate research with clinical care as part of their workload. Collaborative Research Agreements established by IARC support joint research projects and through these encourages training for African scientists with IARC scientists and other international partners.

One issue that is often overlooked in the operations of biobanks and subsequent training is the need for biobank administrative personnel to be trained on biobank procedures and governance. They also have to be equipped to deal with fiscal expertise in the management of biobank funding grants. Furthermore, receiving training in grant writing such as training programs provided by NIH will permit the biobank to access potential funding opportunities. These personnel may be part of the larger research institute and it is important that they are competent in grants management

including fiscal accountability, data management, research oversight, and submission of grant applications. There is, in fact, the Association of Research Administrators in Africa set up in 2009, which aims to establish a hub of excellence for research administrators and fill the gaps of research administration in Africa [71].

It is also an important exercise to provide some manner of educational program to those that have the ability to help mold regulations and legislation within the low-income country. It is not unusual that these professionals do not have experience in biobanking or indeed in the understanding of the ability of biobanks to improve research and in turn to improve health care within their country. Providing training to ethics committees and institutional officials opens the door to providing the biobank with a foundation on which biobank sustainability can be built. This can also help ear mark local funds to provide the infrastructure for national biobanks in addition to helping regulations to facilitate the process.

18 Standards and Harmonization

Materials and data are the basic fuel of all clinical research and their quality directly affects the quality of the resulting research both in terms of reliability and reproducibility. Standard operating procedures (SOPs) have been developed for all processes of the biobank to ensure this quality. Similar to the constrictions of the physical infrastructure, these standards and quality parameters also determine the materials collected and the methods of conservation. Ensuring quality means adhering to these standards, but in a low-income country hampered by various conditions, these standards must have a lowest common denominator for, and be defined by, pre-analytical indicators that represent the stored sample to ensure that the quality is consistent. This is particularly important in low-income contexts as it provides the parameters for sample quality evaluation where collection conditions are more variable. The more quality data registered, the more a sample, even if not collected in optimum conditions, such as those in many LMICs, can be qualified. As such, in LMICs the amount of data registered for a sample can be a determining factor in the process of biobanking. Not only does this provide detailed definition of the samples and the resulting research, it also provides the ability for harmonization among different biobank samples, as it is impossible to dictate that all biobanks follow the same standard operating procedures, particularly in low resource contexts where conditions and facilities determine the applicable procedures. The ability to harmonize biobank samples from these countries permits them to enter the global arena and provide inter-operability between these banks and those in developed countries. In the same way, standards and quality assurance apply to biobank sample associated data as it provides a more complete definition of the biological material. Associated data comprise clinical information, histological-pathological data, and other patient related information. Harmonization of this data is as important as various ontologies tend to be used in different clinical environments and even more so in low-income countries.

19 Networks

Biobank networks are important to ensure the ability to accumulate the statistically significant numbers necessary for research and prevent fractious collections in low and middle-income countries that result in many valuable samples remaining unused by the broader research community.

Networks serve not only as a method to provide a common catalogue but also to provide education and training; policy, legislation, regulations; human resources development; technology transfer and infrastructure development. National networks are an excellent way to provide standards to independent biobanks in a country.

A case in point is the South African Biobank Network that plans to integrate universities, forensic laboratories, clinical trial laboratories and researchers of the nine provinces. The plan is to extend this national network to other African countries in the Southern African Development Community of Botswana, Zambia, Mozambique, Angola, Swaziland and Lesotho, and later to other countries in Africa such as Ghana, Nigeria, Libya, and Egypt. The way forward is through fostering collaboration at a national level through Departments of Health, Departments of Agriculture and Departments of Environmental Affairs [44]. Another example is the Israel Biobank Network, which is a laboratory based national network of biobanks set up with a minimum budget, and follows a hub and spoke model similar to that of the European BBMRI-ERIC network [45].

The development of continental biobank networks in LMICs help foster relationships for future cooperation with biobank members and facilitate research cooperation in countries that could encourage more research exchange.

The Low-and Middle-Income Countries Biobank and Cohort Network (BCNet) initiative by the International Agency for Research on Cancer (IARC), arose from the realization that despite improvements in developed countries, population cohorts and biobanking facilities are either underdeveloped or non-existent in LMICs. Thus, public health professionals and decision-makers lack the scientific evidence about cancer causes and control measures that are needed to set up targeted and cost-effective action plans within their health-science systems. In addition, many LMICs have yet to develop standard guidelines and protocols regulating the sharing and use of biological samples for research purposes. In this context, IARC set up BCNet as an opportunity for LMICs to work together in a coordinated and effective manner and jointly address the shortfalls in biobanking infrastructure and other shared challenges, including ethical, legal and societal issues (ELSI). In addition, the network will facilitate the sharing of resources (e.g. expertise, protocols) and the development of joint projects, strengthening the competitiveness of the Low and Middle Income country biobanks in applying for international funding. BCNet was established together with the US National Cancer Institute-Center for Global Health and other international partners to leverage existing infrastructure to support the development of appropriate facilities while building new capacity and competencies. A network such as BCNet is important in promoting cancer control in LMICs through educational and methodological support in building and developing international

state-of-the-art research infrastructures for cohorts and biobanking facilities in these countries. The participation of both members from LMICs and partners from international organizations and societies with interest in biobanking development in resource constraint settings provides the possibility of exchanging knowledge and improving harmonization [46].

20 Sustainability

One challenge that has existed globally has been the lack of recognition of biobanks as an essential part of research infrastructure and as such most funding agencies have been slow to provide dedicated funding for the creation of biobanks. While external funding can help especially for the start-up phase, this funding is usually project-specific, funded as part of the sample collection effort and limited in time. Even initiatives such as the H3Africa that have dedicated funding for biobank infrastructure are only medium term [27]. Medium and long-term sustainability are the real problems.

Stakeholders are important to the discipline of biobanking as they facilitate the ability of a biobank to operate and guarantee its sustainability. Stakeholders are all of those involved in, and with a vested interest in, the biobank. While this must always include the donor and, in LMICs where community and tribal hierarchies abound, the group leaders, it also needs to have institutional involvement. It is important that there is buy-in for the biobank at these echelons of power to ensure potential continuity once the initial setup funds have been exhausted. Institutional ownership is primarily emphasized, as institutes are required to commit resources to ensure the continuation of biobank administration activities and the integration of these activities into the overall strategic plan [72].

It is also vital that there is governmental commitment to ensure the potential continuity and sustainability of the biobank once the initial setup funds have been exhausted, but this may be undermined by political instability in emerging countries, as well as the difficulty of prioritizing this type of investment among the many other unmet needs in healthcare. Institutional commitment may be as simple as dedicating space or providing access to processing laboratories. Perhaps even more vital is the guarantee of permanent technical personnel whose presence essentially ensures the continuity of the biobank.

Long-term sustainability for biobanks in low resource contexts will no doubt require the support of industry and pharmaceutical companies who also will have to change their business models to meet the changing requirements of personalized medicine. Biobanks that are integrated into healthcare infrastructure can benefit most from this, and in fact both systems can bootstrap off each other to improve processes and mitigate costs. Creating a business model for the biobank that incorporates some services will also assist the biobank in generating operating revenue that will ensure its sustainability.

21 Conclusion

In order to address the inequities of the global burden of disease, there is a need for evidence-based programs of prevention, early diagnosis, treatment and palliative care. The creation of biobanks in low resource contexts, that carry 90% of this burden, can play a fundamental role in the discovery of new targets for therapy and development of novel drugs to address the underlying environmental, somatic and genetic variations of population in these countries that have been largely overlooked in the era of stratified pharmaceuticals. It is, of course, vital that the processes and procedures for biobanking in these contexts are harmonized with those of the developed world to ensure that they can be integrated into the larger context of global biobanking in the twenty-first century to guarantee their participation in the shift towards truly personalized medicine. Biobanks provide a unique opportunity for low and middle income countries to use the biobanks to attract research interest, international collaboration and industry, all of which serve to evolve healthcare in these countries into a mature system that can adequately respond to the population's needs. Biobanks are the currency for representation of populations in low-income countries in scientific research. They can provide populations in these regions with the equitable opportunity for research to include their particular genetic and environmental make-up and provide solutions that are also applicable to them.

Lack of foundational healthcare infrastructure and services, aligned with the need for biobank infrastructure to be compatible with local conditions and conservation methods, affect the development of the biobank and its ability to respond to specific research requirements. Underlying this is the insufficiency of medical personnel expertise, trained technicians and researchers to provide diagnostic data annotation, to execute the basic biobanking services and biobanking research. Inconsistent or absent regulations and ethical guidelines to encompass cultural and religious limitations for acquiring samples/information and low prioritization or lack of understanding of the importance of biobanking in a public health context by government officials and policymakers impede benefit sharing and sustainability.

It is first and foremost critical that legislators and policy makers understand the role of biobanking in clinical research and ensure the development of adequate governance to guard the interests of the general community and the research potential. The creation and harmonization of legal and regulatory guidelines, sustaining new models that address the varying cultural and social structures that exist in low resource countries, will protect the patrimony of these countries and improve public perception to biobanking. These models must consider benefit sharing for biobankers, researchers and contributing populations with returns that could take the form of training, collaboration, publications, technology transfer, research data, and health care improvements such as technology transfer.

Operational challenges lie in the ability to create infrastructure and procedures that are adapted to meet the environmental and variable conditions of low and middle income countries but that do not conflict with methods and standards used in

developed countries. One way to achieve this is to define the condition and the context of samples by describing their pre-analytical information and associated clinical-pathological data. Integration with the healthcare system and the availability of personnel is vital as their contribution and understanding of the importance of these parameters is essential in low resource contexts where sample collection conditions are variable. Making this variability transparent through adequate annotation will ensure that this variability can be translated into harmonized biomaterials that can contribute to the global arena and thus attract research and industry investment, which in turn can provide answers to the immature healthcare systems in these low resource contexts.

Sustainability remains a major challenge in low-income countries where economic resources are lacking to build or improve healthcare and research infrastructures. With the exception of unique initiatives for financial support to create research infrastructure, most grants are related to research projects and all are short and medium term. Institutional investment is required to ensure some form of ongoing sustainability by maintaining biobank infrastructures with permanent technical and scientific personnel. Healthcare and education strategists in these countries need to consider biobanking as a strategic activity for research and innovation in biomedicine and an investment in improved healthcare [2].

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Chinese Biobanking Initiatives

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Abstract Due to the requirement for comprehensive clinical research efforts in China, the importance of biobanking in modern clinical research is outlined in this overview. Hospitals, universities and research institutes have been well organized as fundamental resources for Chinese biobanking initiatives and the resulting biosample collections. Here, a brief history and time line of development of biobanking in China will be introduced, as well as strategic designs for future biobanking development.

Keywords Biobanking • Biobank • Biobank networks • Clinical biobanking • Hospital integrated biobanks • Personalized medicine

1 Introduction

As early as 1994, for the storage of large numbers of immortalized cell lines from Chinese ethnic groups [1], the Chinese Academy of Medical Sciences launched the first "biobank" project in China (Fig. 1). Following that initial effort, in 1998, with the further development of biobanking initiatives, the Ministry of Science and Technology (MoST) and the Ministry of Health (MoH) of China drafted *Interim Measures for the Administration of Human Genetic Resources* [2] to manage human genetic resources. However, more robust biobanking activities in China actually

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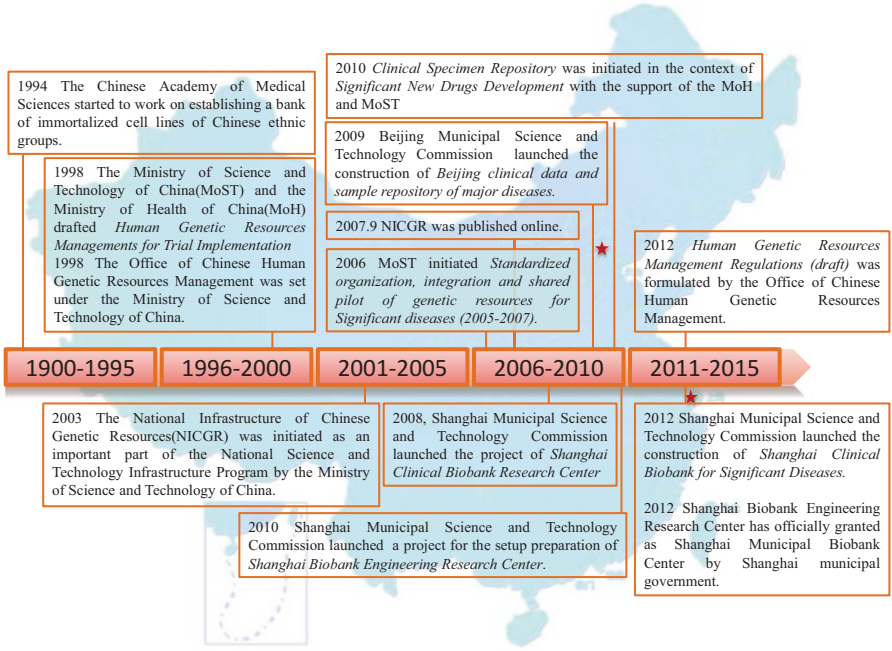

Fig. 1 Timeline of Chinese biobanking development

began more recently, in about 2005. Accordingly, the more comprehensive *Human Genetic Resources Management Regulations (draft)* were formulated by the Chinese Human Genetic Resources Management Office in 2012 [3], which was established under the MoST as well.

In July 2003, the National Infrastructure of Chinese Genetic Resources (NICGR) was initiated as an important component of the National Science and Technology Infrastructure Program by the MoST, and the resource was open for access through the internet in September 2007. Similarly, the MoST initiated another project called *Standardized Organization, Integration and Shared Pilot of Genetic Resources for Significant Diseases (2005–2007)*, aiming to integrate genetic resources of selected diseases. Importantly, the sharing mechanism was also considered as a crucial aspect for biobanking initiatives within the scope of this project [4].

In line with the *Outline of the National Program for Long and Medium-Term Scientific and Technological Development (2006–2020)*, a major science and technology project on *Significant New Drugs Development* was launched [5]. In 2010, the project called *Clinical Specimen Repository* was initiated in the context of *Significant New Drugs Development,* with the support of the MoH and MoST [6]. Accordingly, MoST published the *Mega-projects of Science Research for the 10th Five-Year Plan* in 2011, where *construction of a large human genetic biobank for biological samples, specimens, and patient cases and a sharing service system* became a key goal. Through further development of shared major science and technology infrastructure, China is dedicated to enhancing innovation capability in biotechnology.

Beijing, Shanghai and Shenzhen are the leading locations for the construction and development of Chinese biobanks, as many biomedical research centers/institutes and clinical facilities are located in these cities. Currently, a wealth of clinical samples are preserved as medical resources and many facilities, such as hospitals and universities, are equipped with the capability for high-quality technologies for sample processing, storage and utilization. The project of *Significant New Drugs Development*, as mentioned previously, was led by Beijing Union Medical College Hospital, together with another nine leading research-based hospitals, e.g., Beijing Institute for Cancer Research, the Chinese Academy of Medical Sciences Fu Wai Hospital and Peking University First Hospital. The biobanking project has focused on sample collections for four disease categories, i.e., malignancies, cardiovascular and cerebrovascular diseases, metabolic diseases and neurodegenerative diseases. In 2009 the Beijing Municipal Science and Technology Commission also launched the construction of the *Beijing Biobank of Clinical Resources* led by Capital Medical University, Tiantan Hospital, Beijing You An Hospital and nine other local research hospitals with distributed construction tasks for cardiovascular diseases, AIDS, emerging infectious disease emergencies, diabetes, cancers and five other disease categories [7].

Biobank construction has also been paid a significant amount of attention by the Shanghai municipal government. In October 2008, the Shanghai Municipal Science and Technology Commission (SMSTC) [8] launched the *Shanghai Clinical Biobank* project, led by the Shanghai Clinical Research Center (SCRC), together with the Shanghai Chest Hospital, Fudan University Cancer Hospital, Shanghai Children's Medical Center and Shanghai Chang Zheng Hospital. In May 2010, SMSTC launched another project to commission SCRC for establishment of an engineering center for biobanking, focusing on the common issues in the field. In August 2012, the Shanghai Biobank Engineering Research Center was officially granted as the first municipal engineering center for biobanking initiatives. Highlighted by the *twelfth five-year plan of strategic emerging industry development* issued by the Shanghai Municipal Government in 2012 [9], biobank and clinical pathological biopositories have become important platforms and major initiatives within the Shanghai biomedicine and medical apparatus and instruments development roadmap. In October 2012, SMSTC launched the construction of the *Shanghai Clinical Biobank for Significant Diseases*, also called the Shanghai Clinical Biobank Project, sponsored by Shanghai Shen Kang Hospital Center, and with Shanghai Biobank Engineering Research Center as a third-party service provider to build a shared platform in Shanghai based on the their joint medical project, which covers clinical data and samples from major tertiary hospitals.

To combine the traditional biobank and a big nucleotide and phenotypic database together, the China National Genebank (Shenzhen, Guangdong), known as CNGB, was founded in 2011, as a nonprofit institute approved by the central government of China and operated by BGI-Shenzhen [10]. Through collaborative activities between universities, hospitals and scientific institutes that share an interest in biobanking, resource utilization and bioinformatics, CNGB is committed to developing a biobank consortium across China and the construction of an expanding network worldwide, to provide a platform for information sharing and exchange of biobank materials, -omics data acquisition, and multi-omics scientific research.

Working closely with ethical review boards and following the applicable regulations to secure the data, CNGB has set as its principal task integrating the contribution of bioresources data into an -omics database that will support both scientific research and commercial applications, such as translational medicine, breeding and new energy exploitation.

Aside from clinical biorepositories, in a large cohort study, together with the University of Oxford, the Chinese Academy of Medical Sciences launched a *Prospective Study of Chronic Diseases In China (China Kadoorie Biobank)*. As one of the world's largest prospective cohort studies for large populations, the China Kadoorie Biobank will be in operation for at least 20 years [11]. In addition, the Fudan University integrated more than 20 research institutes in China for the core cohort demonstration study of Chinese populations in Taizhou, Jiangsu Province. In 2012, Fudan University also supported the *Large Cohort Key Technology Demonstration Research on Regional Population Health*, in the context of the *National Science and Technology Support Program For Twelfth Five-Year Plan*, aimed at establishing appropriate and key technologies for a large cohort of a healthy regional population, and will probably integrate and share these technologies in a later phase [12].

2 Present and Future

During recent years, the Chinese biobank development has made great progress. Chinese biobanking has laid a solid foundation to promote the development of life science and translational medicine, with the aim of improving the prevention and treatment of major diseases in China. In the future, the Chinese biobanking initiatives will begin with National Biobank Centers as first attempts, which will be the most efficient way to take the biobanking strategies to a practical level. Locations with strong backgrounds of medical science will be given the priority to establish national facilities, for example in Beijing, Shanghai, Shenzhen and other locations. For integrating national comprehensive medical research institutions together with the joint research hospitals, the national biobank centers will be centralized banks, not the largest biobanks in the country but rather as bio-storage institutes for strategically important projects. The national biobank centers will also work as backup repositories for specific bio-samples. A quality management system will be designed for implementation as the standard for Chinese biobanking. That is, a national biobank center will not replace any biobanks in clinical practice, but may serve as a demonstration project for biobank engineering and design in China. As a reference biobank, the national biobank center will not only emphasize biobanking standards, but also introduce cutting-edge technologies into biobanks with the aim of consistency and cost efficiency.

At present, Beijing, Shanghai and Shenzhen have taken the lead in the national biobank construction. For example, the project Clinical Specimen Repository in the context of the major science and technology project Significant New Drugs Development, led by the Beijing Union Medical College Hospital, is the largest clinical biobank in China currently. The project is committed to establishing a national biobank with uniform standards, centralized collection/preservation of

biological specimens, and coordinated utilization. Four major disease categories have been outlined to build a clinical resource database and its corresponding biological repository, and the information network platform. Based on significant demands for the national biological research and pharmaceutical industry development programs, bio-sample collection could be expanded in its scale and types of samples. The operation and management model has been improved as a model for the future standards of the regional biobank construction and operation in China. In 2012, the project obtained the support of the Beijing Economic and Technological Development Zone (Beijing Yizhuang), with an area of 5000 square meters, and funding of ¥200 million (approximately $33million USD). The current plan is to build the clinical resource database and its corresponding biological repository, which can collect more than 200,000 cases, with a total of 100 million samples.

Initiated in Shanghai, the idea of the Clinical Biobank for Significant Diseases (CBSD) is to build a hospital-based biobank, with sample collection decentralized and data stored in a centralized biobank. It focuses on four kinds of disease categories including diabetes, metabolic diseases, cancers, neurological and hereditary disorders. The first People's Hospital, Ruijin Hospital, Zhongshan Hospital and other 21 hospitals made a concerted effort to construct CBSD. Meanwhile, as the third-party service provider, the Shanghai Biobank Engineering Research Center is responsible for the backup of data/samples and to explore technical support, a management services model and shared operational design. Thus, a "centralized and scattered" model was established and a case-centric, clinical and bio-sample information integrated biobank information system was formed. It is postulated that the program can promote the effective utilization of biological samples in a productive way. Based on the disease biobank construction, the population biobank construction will also be initiated in the future. The ideal model is to set up a standardized and sustainable biobank network based on satellite storage supplemented with centralized backup.

As an unincorporated international collaborative institute, CNGB is devoted to the comprehensive collection of biological resources preservation, data generation and establishing a global network to promote information sharing and exchange. Resources to be collected include specimens from humans, animals, plants, microorganisms and marine samples. In addition, a metagenome resource bank which could leverage microbial diversity to support therapeutics and industrialized applications is also included. So far, a number of projects with significant international influence have been initiated by CNGB, such as the 3-Million Genomes Project, the 1000 Mendelian Disorders Project and the 1000 Fish Transcriptome Project (Fish T1K). CNGB has collected more than 1.5 million traceable biospecimens, stored 20 PB (petabyte) data and released three approved standards.[1] In June 2013, the CNGB ethics committee was established.

[1] Animal Germplasm Repository Construction and Management Norm(Shenzhen Standarlized Guiding Document No. SZDB/Z 91-2014), Human Biorepository Construction and Management Norm (No. SZDB/Z 92-2014) and Biological Genetic Information Database Construction and Management Norm (No. SZDB/Z 92-2014) were published in January 23rd 2014, which were collaboratively written by Shenzhen Administration of Market and Quality Supervision and Management, CNGB and Shenzhen Institute of Standards and Technology.

The National Biobank Centers will establish a replicable biobank model with reasonable standards, quality management systems, efficient utilization of samples, and mutually beneficial mechanisms for sharing, internationally compliant ethical norms and intellectual property rights. Accordingly, other cities in the country, e.g., Guangzhou, Chengdu and Shenyang, could follow this path. Over a period of time, national biobank networks can be connected through the gradual integration of existing and planned biobank resources. The protocol for bio-sample sharing can be therefore discussed within an agreed upon framework. With a compatible informatics platform, the communication between the biobanks will be facilitated by national biobank networks. On the other hand, the harmonization of biobanks will be improved and national biobank standards can be promoted.

Meanwhile, for a professional biobank, long term support and financial planning are crucial. The Chinese government will guide biobank development through major national programs related to a variety of diseases. The major national research programs will provide comprehensive funding to cover the whole life span of biosample collection, transportation and long-term storage. Therefore, the development of national biobank centers will be comprehensive, and the resources of national centers will be more sustainable with the inclusion of cost recovery and independent government support.

Concerning ethical, legal and social (ELSI) issues, the updated version of "Administration of Human Genetic Resources" has been under review. The importance of regulation of human bio-samples has been emphasized by the MoST of the People's Republic of China. "The guideline of bioethics in China biobanking" [13] was also drafted to recommend practical regulations for biobanking ethics in China. In line with these recommendations, the timetable of biobank-relevant legal requirements will be scheduled as soon as possible to align with the China biobanking strategy.

Furthermore, involvement and engagement of the public is of great importance in biobanking. The public trust in medical institutions has become a serious issue for biobanking in China [14] The public awareness will be raised and continued participation, trust, and support from the public will be emphasized for biobanking development. The biobank system will be designed for clinical science, which serves the population in China, including donors themselves. In addition, through these developments professional education and training will be valued and enhanced as well.

In conclusion, with the rapid development of life sciences research, China will make additional investments in biobanking. Although there are universal challenges that Chinese biobankers are confronting, such as the underuse of samples, ethical, legal, and social issues (ELSI), establishment of compatible data management and international standards and other issues, the potential significant advances in translational medical research cannot be overestimated. In the near future, the top-level design, the capability of management and national biobank sustainability will be a major focus for the Chinese Biobanking Initiative. The Chinese Biobanking Initiative will support modern clinical research, help address important health issues, and ultimately serve the development of the national economy and the people's livelihood.

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Biobanking in Africa: Opportunities and Challenges

Jim Vaught

Abstract Biobanking and its associated policies and procedures for managing biological specimen collections are critical to the success of a variety of research endeavors. Several international organizations have produced best practices which cover the important technical and ethical-regulatory issues that are important for the collection and management of biospecimens and associated data. The expanding and global nature of biomedical research has resulted in disparities in biobanking practices among high-income countries (HIC) and low- and middle-income countries (LMIC). In Africa, projects such as H3Africa and B3Africa have resulted in new and promising advances in biobanking infrastructure and the creation of biobanking networks. However, the initiation of such projects has highlighted some of the challenges faced by biobanks in Africa, from both the technical and ethical-regulatory perspectives.

Keywords Biobanking • Africa • Low and middle income countries • H3 Africa • B3 Africa • Sustainability

1 Introduction to Biobanking

Biobanking[1] involves the collection, processing, storage and use of biological specimens for research purposes. For the purpose of this chapter we will generally concentrate on biospecimens[2] collected for research into the etiology, diagnosis and treatment of cancer, although most of the issues discussed apply to infectious

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[1] Biobanking and biobanks may also be referred to as biorepositories, biological resources or biological resource centers (BRC).

[2] Biological specimens or biospecimens can be solid tissues, fluids e.g. blood, urine, saliva.

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disease biobanking efforts as well. Historically, early biobanks emerged from the collection of samples by surgeons and pathologists for diagnostic purposes. Thus the earliest biobanks evolved from collections housed in pathology departments. In the United States, the Armed Forces Institute of Pathology (AFIP) collection was initiated during the American Civil War [1]. A similar example in Africa is the Kampala Cancer Registry (KCR), which is situated in the Department of Pathology, School of Biomedical Sciences, Makerere University College of Health Sciences and has maintained tissue samples collected for diagnosis dating back to 1954 [2].

Biobanks may be small collections within a pathology laboratory, a few freezers in a basic or clinical research department, or a large government or commercial operation with hundreds of freezers and millions of biospecimens [3]. Biobanks may house tissues in the form of formalin-fixed, paraffin-embedded blocks or in the frozen state. Fluids such as blood and blood fractions (serum, plasma, buffy coat), urine and saliva are also collected. The type of biospecimens collected and the processing and storage conditions chosen by researchers depend on the intended analyses, e.g., for cancer biomarker development [4]. Pre-analytical variables such as ischemic time, freeze-thaw cycles and other factors may affect the quality of the samples and result in misleading laboratory data [5]. The field of "biospecimen research" has emerged to study and mitigate such pre-analytical factors [6].

As biobanking has grown and expanded globally, a general trend toward "professionalization" has emerged. Organizations such as the International Society for Biological and Environmental Repositories [7], the European, Middle-Eastern and African Society for Biopreservation and Biobanking [8], the Biobanking and BioMolecular Research Infrastructure [9] and Biobank Cohort Building Network [10] initiatives are all promoting biobanking education, standards development and research. Graduate level biobanking degree programs will result in a new generation of biobankers [11]. Before these developments over the past 20 years, biobanking was a secondary career for pathologists and other research professionals who created and operated biobanks, and developed practices on an empirical basis to fit their needs.

The trends toward more organized and professionally-managed biobanks have created new opportunities for international cooperation and collaboration [12, 13]. However, such international collaboration requires standard practices for collecting and exchanging biospecimens and data (see next section, Biobanking Best Practices). In addition, the larger biobanks now usually will benefit from developing a business plan and a strategy for long-term sustainability, i.e., in the event of funding limitations [14]. In terms of the technical aspects of biobanking, emerging technologies for collecting, processing and storing sample need to be followed closely, as the success of a research project may depend on developing new evidence-based practices [3, 15]. Even more difficult to manage are the ever-changing ethical and regulatory aspects of biobanking, including informed consent, privacy, intellectual property and sample and data access policies [16–18].

A reform of the European General Data Protection regulation (GDPR) has been proposed and discussions at the European Trilogy (Parliament, Council and Commission) are ongoing. The reforms aim to strengthen and unify data protection for individuals within the European Union [19]. The GDPR also addresses export of personal data outside the EU which poses more challenges that will need to be managed by biobanks.

A "Q & A" article in Clinical Chemistry in 2014 [13] outlined "Critical Issues in International Biobanking," including: quality management; sustainability; centralized versus distributed biobanks; communicating the value of biobanks; data sharing; and the management of return of research results and incidental findings (see Challenges to Biobanking in Africa). As discussed in the following sections, such issues are not unique to biobanking in Africa, but are among the challenges that must be managed for the long-term success of biospecimens-based research on the continent.

2 Biobanking Best Practices

As mentioned in the last section, as biobanking has grown into a global enterprise, it has become necessary to develop best practices to control the technical and ethical-regulatory aspects of biospecimen management. Prior to the publication of such best practice documents, it was customary in biobanks as well as, for example, pathology laboratories, to develop biospecimen collection, processing and storage protocols to fit local needs. However, as problems emerged with sample and data exchange among collaborators, a number of international organizations published best practices, which have been widely adopted over the past 15 years. Among the organizations which have led in developing such documents are IARC [20], ISBER, OECD and others. Several comprehensive reviews have outlined the evolution of such guidance documents [21, 22].

Biobanking best practices are generally divided into technical and ethical-regulatory (also referred to as ELSI or ethical, legal and social issues) recommendations. Box 1 shows the table of contents from the U.S. National Cancer Institute Best Practices for Biological Resources [23]:

Box 1
The following shows the major contents headings from the U.S. National Cancer Institute *Best Practices for Biospecimen Resources.*

A. Scope, Applicability, And Implementation.
B. Technical And Operational Best Practices.
B.1. Biospecimen Resource Management And Operations.
B.2. Biospecimen Collection, Processing, Storage, Retrieval, And Dissemination.
B.3. Quality Management.
B.4. Biosafety.
B.5. Collecting And Managing Clinical Data.
B.6. Biospecimen Resource Informatics: Data Management And Inventory Control And Tracking.
C. Ethical, Legal, And Policy Best Practices.
C.1. Principles For Responsible Custodianship.
C.2. Informed Consent.

(continued)

Box 1 (continued)

C.3. Privacy And Confidentiality Protections.
C.4. Access To Biospecimens And Data.
C.5. Intellectual Property And Resource Sharing.
C.6. Conflicts Of Interest.

Box 2 Informatics: The Electronic Glue of the Biobank (Reprinted from Vaught, 2016) [3]

Biobanks are dependent on information systems for a number of critical functions. At every step of the processes of receiving, shipping, collecting, processing, storing and retrieving specimens from storage, the samples must be accurately tracked, with every movement and process recorded. Chain of custody is an important concept in biobanking. Bar coding or RFID tracking are necessities. Freezer inventory systems are necessary to maintain up to date information on all steps of storage and retrieval. Laboratory information management systems (LIMs) have been adapted to biobanking applications and have been widely adopted.

The annotation of specimens with clinical, demographic and analytical, as well as sample handling data, contribute to their long-term value. Standards for collecting and transmitting specimen data are critical to the biobank's success. Developing a minimal set of data elements for each biospecimen research project should be an early step in project planning. There are some issues which must be resolved in order for biospecimen research collaborations to be successful. Often informatics systems developed for one institution cannot communicate with other institutions without the development of an interface to allow the systems to be interoperable. Biobanking best practices provide general guidance on overcoming such obstacles.

The technical and operational recommendations from IARC, ISBER, OECD and NCI provide varying levels of details concerning collection, processing, storage and shipping practices, as well as the necessary supporting informatics systems. (See Box 2).

For a review of biobanking practices specific to projects being conducted in Africa, see the chapter by Mendy et al. "Biosampling and Biobanking," in the Handbook for Cancer Research in Africa [24]. The IARC, U.S. NCI and ISBER best practices documents also provide specific technical recommendations which may be helpful depending on the biobank and researchers' goals. As indicated above, technical best practices must evolve over time as new technologies emerge and biospecimens methods research result in the adoption of evidence-based practices [15]. Note however that with multiple best practices documents available, and

often-conflicting research results, it has been difficult to harmonize such recommendations on an international basis [12, 13].

Even more challenging than developing and staying up to date with biobanking technical practices are the issues faced with ELSI practices [16, 17]. As indicated by the NCI Best Practices contents in Box 1, the issues cover a broad range of ethical and regulatory recommendations. However, the policies are continually changing and are often controversial. For example, the rules concerning informed consent and privacy differ among countries. And such rules and regulations can change in ways that affect the ability of researchers to collect the biospecimens they need. Other related ELSI practices include: planning for long-term custodianship; policies for access to specimens and data; controlling conflicts of interest; and managing data and sample sharing and intellectual property through, for example, material transfer agreements [23].

A special aspect of biobanking that has emerged over the past few years is the importance of developing strategic and business plans, and planning for the long-term sustainability of the operation [25, 26]. During economic downturns and in particular for biobanks in low resource countries it is important to develop such plans. Recommendations related to business plans and sustainability have appeared in a number of editorials and review articles [14, 25].

3 Biobanking in Africa: Examples of Projects

The chapter by Mendy et al. in the Handbook for Cancer Research in Africa [24] noted the following:

"The global total of new cancer cases is projected to increase by 60% to 21 million annually by 2030, with an estimated 13.1 million deaths from cancer yearly. About half of these cancer deaths will occur in low-income countries and more than 80% of these in African countries."

Given biobanking's central and critical role in basic, translational and clinical cancer research, developing workable standards for biospecimen management in African countries is necessary. Early biobanks in Africa were developed due to the need to collect samples during the AIDS epidemic [27]. More recently the Ebola epidemic in western Africa led to additional biobanking needs. Thus much of the early and current biobanking activities in Africa have resulted from the spread of emerging infectious diseases, as well as more long-term issues concerning tuberculosis and malaria [27] (see Chapter "Biobanks in Low Resource Contexts", Box 3).

An example of an institution in Africa that had adopted biobanking as a research platform since the early 1970s is the Medical Research Council Unit in The Gambia West Africa [28]. The MRC biobanks have biospecimens collected for research on infectious and chronic diseases since the early 1970's See Chapter and has provided the facilities for one of the first national DNA bank in Africa [29].

Recently two projects have been funded which will result in additional progress in biobanking and research infrastructure in Africa: H3Africa (Human Hereditary and Health in Africa) and B3Africa (Bridging Biobanking and Biomedical Research

across Europe and Africa). The H3Africa program, jointly funded by the Wellcome Trust and the U.S. National Institutes of Health (NIH), will study the genomic and environmental determinants of a variety of diseases [30]. The program required the development of a biobanking network among several African countries (see Chapter "Biobanks in Low Resource Contexts", Box 4). A review by Abayomi et al. noted that developing harmonized technical and ethical standards among the project's network partners was a challenge. In general, the lack of biobanking standards and infrastructure in Africa slowed the initial progress in developing the H3Africa network [31].

B3Africa, the Bridging Biobanking and Biomedical Research across Europe and Africa project, funded by BBMRI-ERIC [32], aims to "implement a cooperation platform and technical informatics framework for biobank integration between Africa and Europe. The collaboration harmonises the ethical and legal framework, biobank data representation and bioinformatics pipelines for sharing data and knowledge among biobanks and allowing access for researchers from both continents."

4 Challenges to Biobanking in Africa

Projects such as H3Africa and B3Africa will result in improved conditions for biobanking and biospecimen research in Africa. However, currently the situation in Africa and among LMICs elsewhere is indicative of the challenges faced in such countries. In a survey conducted by IARC among LMICs in Africa, Asia and Europe [27] it was determined that although there were some exceptions, in general biobanking in LMICs were lacking in the technical and ethical-regulatory standards and infrastructure practiced in HICs.

In terms of technical issues, many of the challenges to successful biobanking among LMICs in Africa relate to infrastructure. The availability of up to date processing and storage equipment is sometimes lacking. If the equipment is available then other issues may interfere with its proper use, such as intermittent power outages [31]. As noted by Fleming et al. in The State of Oncology 2013 [33, 34] there is also a shortage of trained pathologists in LMICs, which presents a major obstacle to collecting high-quality samples and otherwise developing well-managed biobanks. The problem is particularly acute in sub-Saharan Africa. The shortage of pathology services not only affects the ability to collect samples for biobanking. The quality of patient care is also affected in that tissues are often not collected for diagnostic purposes.

Biobank sustainability is also an issue among African biobanks, as it is among all LMICs. Even among more well-developed biobanks in developed countries, biobanks are generally not self-sustainable without significant contributions from government and/or institutional sources [25, 26].

As noted by Abayomi et al. [31], ethical, legal and social issues have been difficult to coordinate and harmonize for biobanking initiatives in South Africa, which has a relatively well-developed research infrastructure. For LMICs in Africa the situation is even more complicated. As noted by Mendy et al. [27] in an assessment of biobanking practices in 26 LMIC centers:

"ELSIs are dealt with by various mechanisms in the different ethics and scientific committees in more than 90% (24/26) of the centres. These committees are responsible for reviewing and approving research activities. However, ELSIs specific to biobanking or biobank projects are usually not included in the committees' review processes, and this is an important challenge in biobank governance in LMICs. For example, most centres do not have patient-consent procedures for the systematic storage of postanalysis clinical samples for future research. Informed consent is project-specific, and broad consent, which would enable efficient use of biobanking resources, is not usually obtained from participants."

Going forward, African biobanking practice is expected to improve as the public and researchers become more educated in best practices (see next section, Biobanking Educational Efforts in Africa), and biobanking networks are further developed to support multi-country projects.

5 Biobanking Educational Efforts in Africa

In addition to biobanking infrastructure issues which are inhibiting research progress in LMICs, there is a general lack of biobanking knowledge among the public and researchers. A number of international organizations have increased their efforts to identify issues and conduct workshops to increase awareness and provide training opportunities.

- **IPRI:** As noted in its mission statement IPRI has "the broad goal of contributing to the improvement of health in populations worldwide".and "aims to increase prospects for prevention through training, education, prevention research and research into causes worldwide with a focus on low and lower-middle income countries." For a discussion of biobanking in Africa, two chapters from the IPRI book "The State of Oncology 2013" [33] are instructive: "Lack of Pathology in Low Income Countries" [34], and "Biobanks: Central Importance and Standards" [35]. In addition, IPRI hosts an annual National Cancer Institute Directors conference, where participants from multiple LMICs, including Africa, meet to discuss their research initiatives and challenges.
- **IARC:** IARC has supported biobanking activities for many years, including the European Prospective Investigation into Cancer (EPIC) [36], which involved creating a biobanking network centered in Lyon and involving multiple sites in Europe. As noted above IARC investigators have published a number of articles concerning biobanking operations and challenges in LMICs, including Africa [24, 27].
- **BCNet:** BCNet is the LMIC Biobank and Cohort Network, and is a cooperative effort among IARC, the U.S. NCI Center for Global Health and other international partners. BCNet has engaged in a number of training effort in LMICs and has recently partnered with ISBER to provide online training for ISBER's Best Practices [7].

- **BBMRI-ERIC:** BBMRI-ERIC supports biobanking educational activities through its annual Hands On Biobanking conference [37], and has recently partnered with ESBB to host annual biobanking meetings.
- **ISBER:** ISBER's Best Practices are available on the Society's web site, and ISBER has developed a Regions program, which includes organizing biobanking efforts in the Europe, Middle East and Africa (EMEA) Region (ISBER Strategic Plan). ISBER's annual meetings attract members from Africa as well as participants from multiple countries.

6 Conclusions and Future Directions

With the recognition that standardized biobanking infrastructure and practices are critical to the success of basic, translational and clinical research, and that international collaboration is now the norm, biobanking in LMICs in Africa and elsewhere will begin to become more in line with practices in HICs. However, there are a number of challenges that LMIC biobanks will need to overcome.

The following are some of the current trends and ongoing biobanking challenges in Africa:

- Other than large projects such as H3Africa and B3Africa, government and institutional support for biobanking will be necessary for long-term sustainability.
- Biobanking infrastructure upgrades will be necessary, including buildings and equipment, as well as measures to control the effects of power outages.
- Important initiatives by BCNet, IARC, IPRI and BBMRI-ERIC will be providing important training tools and infrastructure support.
- Biobanking workshops to discuss and resolve regional issues in Africa are becoming more frequent, hosted by recognized international biobanking organizations, such as ESBB and BBMRI-ERIC.
- The development and management of biobanks needs to follow best practices which cover technical and ELSI recommendations as well as the necessity for comprehensive governance policies for access and long-term sustainability.
- The current lack of sufficient numbers of pathologists and other professional biobanking personnel should be improved through training programs and biobanking workshops.
- New and alternate technologies and evidence-based biobanking practices will need to be adopted to meet the special needs of African biobankers.

The above recommendations will require time to yield results. And the challenges discussed in this chapter are not unique to Africa or to LMICs. International standardization and harmonization are issues faced in all biobanking endeavors. The major biobanking organizations such as ISBER, BCNet, IARC and BBMRI-ERIC are working to overcome these obstacles, and all are engaged in initiatives on multiple continents [12, 13].

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Cryobanking Biomaterials from Wild Animal Species to Conserve Genes and Biodiversity: Relevance to Human Biobanking and Biomedical Research

Pierre Comizzoli and David E. Wildt

Abstract When considering the topic of biobanking, it is natural to think first about the collection, storage and use of human biomaterials, a process now considered essential for addressing many diseases and medical conditions. But for more than 25 years, systematic gathering and cryo-storage of biomaterials from diverse wild species have been ongoing to save gene diversity and improve captive (*ex situ*) and wild (*in situ*) animal management. Whereas repositories for humans generally are highly specialized toward a targeted medical issue, cryo-storage of non-human biomaterials offers broader opportunities—from helping understand the fundamental biology of unstudied species to enhanced conservation breeding, genomics and veterinary medicine. While promoted for decades, the banking of germplasm, tissue, blood and DNA from wildlife species only recently has been considered by some to be a core function of animal conservation programs. There are commonalities between human and wildlife biobanking programs, including similar needs to harmonize sample and data collection, management and most effective use as well as finding ways to be financially sustainable. We argue here for the need to build bridges between these two 'repository worlds', sharing what we do, addressing the substantial remaining challenges and considering the advantages of a bigger, more integrated field of global biobanking science to benefit humans, diverse species and the planet.

Keywords Endangered species • Ecosystems • Cryobiology • Biobanking • Conservation breeding • Biomedical research

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1 Why the Need for Wild Animal Biobanks?

Understanding and sustaining biological and genetic diversity is a social, cultural, scientific and economic imperative that is key to adaptation and survival in a human-dominated environment [20]. It is apparent that the earth's biodiversity (its wealth of diverse species) is under assault by habitat degradation and loss, overexploitation, pollution, emerging diseases, invasive alien animals and plants and climate change [39]. Besides putting the existence of species at risk, these hazards lead to small, fragmented animal populations that reduce resiliency and adaptability to change, often through the loss of genes that control integrity and fitness. Once a genetic resource disappears, it cannot be recovered. Wilson [41] stated that 'biological diversity is the key to the maintenance of life as we know it'. It is the planet's life support system, regulating local climate and atmospheric quality while absorbing pollutants, protecting watersheds and generating and maintain soils [35]. We depend on organisms daily for food, medicine, chemicals, fiber, clothing, structural materials, energy and recreation. Most of all, ensuring the long-term protection of all species and their genotypes helps maintaining an environmentally functional, healthy planet [39].

But, how do we preserve all biological things? Historically, genetically diverse species have been preserved by protecting large-size natural habitats, a strategy that, while ideal, is insufficient given our growing global human population that now exceeds seven billion people. Resource demands by humans doom the idea that all species can survive sustainably and undisturbed in nature. Zoos and aquaria are not the answer due to severely limited spaces in their restricted urban environments—too few acres to manage enough animals. This is now fact as most structured breeding programs in zoos are failing to meet demographic and genetic goals, including retaining at least 90% of existing gene diversity [25]. Thus, while governments determine how to protect and restore habitat, and zoos explore alternative conservation approaches (for example, the advantages of large breeding centers; [40]), there is a crucial unfilled gap—protecting the extant genomes of living species that already are under threat, or are likely to be so soon.

This need actually may be envisioned as an enormous opportunity that can be addressed by establishing and using wildlife biobanks—organized collections of living biomaterials. The value of maintaining data-rich biological samples, including microorganisms, DNA, somatic cells, tissues, blood products, germplasm and embryos, has long been recognized for human health care and agro-industries and is a fundamental component of most basic scientific research. Nowhere are activities booming more than in human biobanking for clinical, reproductive and regenerative purposes, including in the rapidly growing biomarker field where DNA sequences, labile RNAs, peptides and antibodies are used for disease surveillance, forensics, medical diagnoses and diverse therapies [1]. But the benefits of long-term biomaterials preservation extend far beyond traditional animal health issues. For example, the storage, movement and use of genetic materials (including sperm and embryos) will be key to meeting the need to double global food production by 2050 (http://www.fao.org/news).

The idea that these genome banks should exist for more than humans, livestock and crops is not new. The U.S. National Academy of Science declared in 1978 that 'what is done for domestic species should be done for all species'. Similar proclamations also were made decades ago by the U.S. Agency for International Development, the U.S. Congress' Office of Technology Assessment and the National Science Foundation (see review [36]). Subsequent advocacy and sound justifications have been provided by various laboratories [10, 18, 34, 35, 37]. First, there is the 'insurance factor', that is, protecting what we have now—all species and all existing gene diversity. Small populations of endangered species are especially vulnerable to events beyond inbreeding depression, including environmental catastrophes and epidemics. This is especially relevant as most of the earth's biodiversity exists in underdeveloped regions that are particularly sensitive to epizootics and drastic shifts in social and political structure. These resources deserve immediate and thorough protection. Second, having repositories of biomaterials, especially germplasm, can support conservation breeding programs where the goal of producing healthy and sustainable insurance populations is only possible in the face of adequate gene diversity. Currently, such programs exclusively rely on the expensive and unsafe movement of wild animals from one zoo to another for breeding. With biobanks and assisted reproductive technologies (i.e., artificial insemination [AI] and embryo transfer), only germplasm and embryos are moved to maintain the same levels of heterozygosity. Availability of germplasm in the repository also extends the generation interval of individual animals indefinitely, to be re-derived and infused into the living population at any time, 5, 20 or more than 100 years from now. The result is decelerating natural losses in diversity as a result of genetic drift. At the same time, managing a portion of the species as frozen germplasm reduces space needs. For example, even partial reliance on AI with frozen semen could reduce the number of living animals required in zoos and breeding centers by as much as 50% [35].

There now are real-life illustrations of using biobanks for conservation breeding. The iconic giant panda is routinely managed in *ex situ* collections and on a large-scale in China using AI with fresh and frozen-thawed spermatozoa [22]. The black-footed ferret, once the most endangered species in North American, has been recovered by a combination of natural mating and AI [21], including with sperm that has been frozen and stored for up to two decades. A litter of cheetah cubs was produced in a North American zoo by importing frozen sperm from a wild captured male in Africa [37]. There also are many examples of 'milestone' births using frozen-thawed spermatozoa or even embryos ([10, 31]; Fig. 1) with the incidence of success completely dependent on having an excellent understanding of the details of the target species' reproductive physiology [8, 39].

The components of the most valuable wildlife biobanks, of course, extends beyond reproductive cells to include tissues, cell lines, blood products and DNA, all highly relevant to the study and maintenance of biodiversity (Table 1; Fig. 2). Quantifiable amounts of genetic diversity can be determined for every sampled individual to help make informed conservation management decisions as well as improve our understanding of the processes underlying patterns of gene flow,

Fig. 1 Examples of species beneficiating from biobanking efforts (germplasm and other biomaterials) associated with assisted reproduction (artificial insemination, *in vitro* fertilization) or genomic technologies that are integrated into the conservation programs. (**a**) Giant panda. (**b**) Black-footed ferrets. (**c**) Scimitar-horned oryx. (**d**) Cheetah. (**e**) Panamanian golden frog. (**f**) Eld's deer. (**g**) Corals

Table 1 Examples of wild animal species biobanks worldwide

Institution/Consortium	Country	Started	Sample number and type
Smithsonian Institution	USA	1970	>1,000,000 DNA samples, cell lines and germplasm samples from >18,000 species
San Diego Zoo Global Wildlife Conservancy	USA	1976	>25,000 cell lines and germplasm samples from >1000 species or subspecies
Kunming Wild Animal Cell Bank	China	1986	1455 cell lines from 289 species
The Frozen Ark	International consortium based in United Kingdom	1996	48,000 samples from >5500 species
American Museum of Natural History	USA	2001	>28,000 tissue and DNA samples
Conservation Genome Resource Bank for Korean Wildlife	Korea	2002	13,475 tissue and DNA samples from 407 species
BioBankSA	Consortium based in South Africa	2003	>80,000 germplasm samples, cell lines, DNA samples from 500 species
Cryo-Brehm	Germany	2007	Stem cells

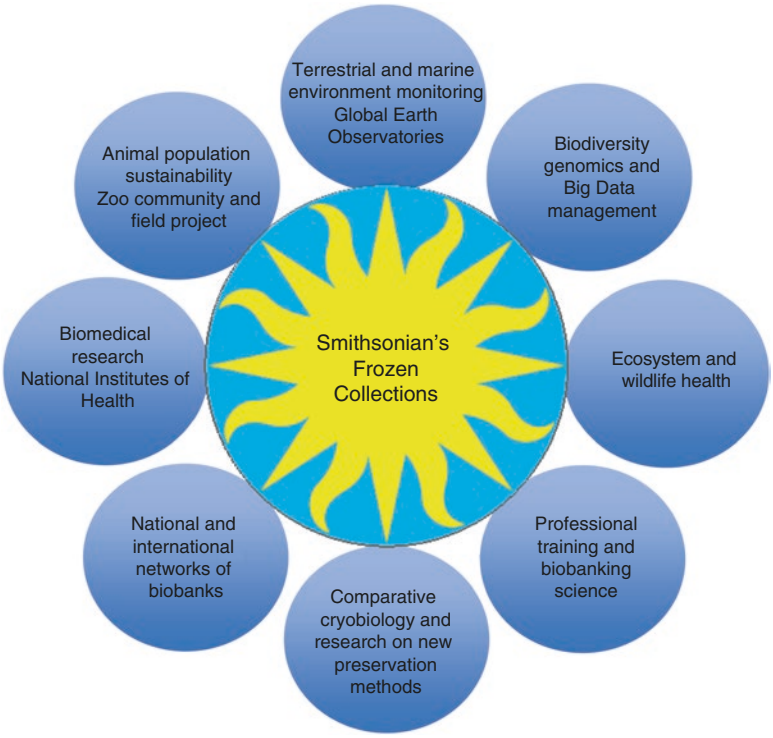

Fig. 2 Smithsonian's frozen collections are at the interface of multiple projects and disciplines related to conservation biology and biomedical research

selection and mating [35]. Blood samples can be screened for clinical chemistries to provide new data on species norms or as sentinel information to identify onset and, eventually, cause of disease outbreaks to speed remedial actions. Samples also are valuable for evaluating reproductive fitness or toxic contamination events in populations (canarydatabase.org). Most importantly, properly organized biobanks can provide open access to qualified researchers who normally work outside the conventional mainstream of wildlife conservation biology. This has the potential for generating vast amounts of additional basic and applied information, especially as advantages of the new 'omics' technologies are realized and directed to stored samples. Genomes of thousands of organisms, including bacteria, archaea and many fungi, animals and plants have been sequenced to begin more thoroughly documenting the earth's abundant bio- and genetic diversity [32]. Genomic data are being annotated, augmented and refined through transcriptomics, proteomics and metabolomics to give us detailed pictures of messenger RNA, protein and metabolite systems and the mechanisms that are controlling life [2].

Other elements also are credible additions to a wildlife bank, including plants, soils, water, ice and environmental DNA, all of which will provide even more information on the health of ecosystems. Examples already are available, including via

the Global Earth Observatory (http://www.forestgeo.si.edu) and Long-Term Environmental Research Network (http://www.lternet.edu) systems that are generating enormous amounts of data to better understand the impact of climate change, pollution and disease. Thus, all types of biospecimens from the planet hold great potential for research, discovery and innovation to find solutions to medical, environmental, energy, security and agricultural challenges ('ecosystem services'; [3]).

Here, we review some of the modern initiatives associated with the collection, storage and use of living biomaterials from wild animal species (DNA bank being considered as non-living sample collections). Of special interest is highlighting the challenges of creating and managing biobanks for such diverse taxa and how these might be similar or quite different from programs in the human medical field. An ultimate goal is to provoke the reader to think about the potential benefits of bigger repository strategies, perhaps through bridge-building between those who gather, steward and use biomaterials from humans and those who are advancing the conservation of wildlife bio- and genetic diversity. There is much to be learned, perhaps resources to be shared and certainly novel technologies (e.g., better, safer, more economical preservation tools) to be explored together.

2 Specificities of Wildlife Species Biobanking

Table 1 is a list of major repositories containing wild animal biomaterials and their location, dates of onset and general composition. While there are large facilities in the USA, other countries also manage biobanks with significant collections representing diverse species and specimens. Among the largest in the USA, is the Smithsonian Institution that curates frozen biomaterials, including DNA, somatic cells, tissues, blood products, germplasm (sperm and oocytes), embryos and aliquots of other animal and plant parts as well as soil components. The contemporary collection is comprised of more than one million samples representing more than 18,000 vertebrate, invertebrate and plant species, all stored in low temperature freezers or liquid nitrogen tanks located at different sites throughout the vast Smithsonian complex. These resources originally were developed to ensure the long-term availability and protection of stored parts and genomes of the world's unique animal and plant species, including from extinct or archeological specimens (i.e., ancient DNA). However, the purpose also is relevant to modern management and conservation activities (Fig. 2). Figure 1 depicts wildlife species where, for example, frozen and banked spermatozoa have been thawed and inseminated into females to produce offspring, either as part of management or for experimental study. While various biobanking activities at the Smithsonian were conducted originally by investigators within individual units, the importance of managing an institution-wide repository now is fully recognized and appreciated, including by administrative leadership. These collective activities currently are conducted under the Pan-Smithsonian Cryo-Initiative that has a mission to promote collaborative stewardship of, and access to, Smithsonian's frozen collections. The advantages of

such a coordinated approach have been significant, including creating stronger justification for more core budget resources for collection and storage as well as for enhanced equipment, staffing, barcoding of individual samples and database development. The latter involves metadata related to sample type, date and locality of collection, Geographical Information System references, collector, voucher information, DNA sequencing, and freezer location (as well as sample location in freezer), among other information items. The Smithsonian is rapidly moving to ensuring that all involved units meet similar best practices in cryo-collection management.

As also presented in Table 1, certain wildlife biobanks have unique characteristics and/or constituencies. For example, the Frozen Ark, launched in 1996 (www.frozenark.org), has a mission to inventory and preserve the genetic material of threatened animal species [6], preferably in the form of living (including somatic) cells. This consortium has a membership platform comprised of zoos, aquaria, museums and universities from the United Kingdom, USA, Australia, India and other countries and has implemented an organized, internationally-linked and properly catalogued repository of genetic material [6]. Currently, member institutions manage more than 48,000 samples representing frozen tissues, somatic cell cultures and DNA from at least 5500 animal species (www.frozenark.org). Some of the newer contributors, such as the German Cell Bank for Wildlife 'Alfred Brehm' (Cryo-Brehm), are contributing stem cells to the collection repertoire (www.emb.fraunhofer.de/en/Uebersichtsindex/cellbank_cryo-brehm.html). Therefore, while early efforts in wildlife biobanking were largely focused on spermatozoa and embryos [18, 37], more recent activities envision significant, near-term opportunities with non-germinal cells. This is logical given significant advancements made in nuclear transfer and stem cell technologies, with somatic cells having potential to be used directly or indirectly for offspring production. The ability to reprogram differentiated somatic cell nuclei into embryonic or germinal cell lineages triggered the original interest in storing somatic genomes about a decade ago [19]. While the technology to convert these cells and DNA into living young has not advanced sufficiently to contribute to 'real-life conservation', there are some enticements to justify continuing such a collection/storage strategy. For example, using new somatic cell manipulations, Ben-Nun et al. [4] have produced embryoid bodies derived from induced pluripotent stem cells (iPSCs) in the silver-maned drill (a non-human primate) and the nearly extinct northern white rhinoceros, the first such cases of induced pluripotency in adult fibroblasts. While many steps away from producing a living youngster, the technique advancements and the new knowledge only have been possible because the raw biomaterials (i.e., germ cells, somatic cells) were available in a biobank. Without this preemptive effort, these genomes would be lost forever, including to whatever new technical approaches may be on the horizon to retain species and genetic diversity and integrity. The same philosophy holds for storing cell lines, the 'gold standard' resource, for genomic studies and the eventual understanding of proteins and epigenetic factors that are regulating unique gene expression [2]. These same thought processes are finding their way into the plant community. For example, the North American Orchid Conservation Center is planning

to freeze-store symbiotic fungi rather than attempt to keep such a massive number of species maintained in culture (http://northamericanorchidcenter.org).

These eclectic biorepositories also are essential for continuing to sort the many challenges remaining in effectively using germplasm and embryos to actually propagate and conserve thousands of species. To-date, most such research has been sperm- and embryo-centric, so there is additional need to focus on female genetic material, especially ova and oocytes [10] as well as their components (i.e., the germinal vesicle; [13]). Due to their size and complexity, ova/oocytes present special cryopreservation challenges. Furthermore, while most research emphasis has been placed on mammals, some of the most interesting issues surround the question of how to store the essential reproductive elements of other taxa, for example, viable fish and amphibian germplasm that are fundamentally complex and cryo-sensitive. In such cases, these problems are being tackled by a host of novel approaches, including freezing gonadal germ cells that later are revived in other individuals of the same or even a closely-related species [10]. However, it has been possible to recover and successfully freeze-thaw mature spermatozoa in at least one toad species [24]. The priority now is developing fertilization methods *in vitro*, which would allow mass tadpole production for reintroductions into nature, thereby allaying some of the conservation challenges related to the deadly chytrid epidemic that has been responsible for multiple frog species extinctions in the past decade [24]. As another example, investigators from our laboratory have successfully processed and then cryopreserved stem cells from coral species, taxa that are experiencing mass die-offs in the world's oceans. After storage in liquid nitrogen, these cells have been thawed and used to create living offspring that would be suitable for repopulating restored marine habitat [15].

In sum, there are substantial ongoing activities throughout certain parts of the world in the collection and storage of many biomaterials from non-human, non-livestock and non-laboratory animals. While most of the emphasis has been on collecting, there is evidence that these specimens are biologically viable. However, clearly there is the need for more research to ensure (1) that samples are being processed appropriately (i.e., after documenting basic cryobiological properties) and (2) that we understand the detailed physiology of every species to ensure that the specimen can be used to give information or produce a healthy offspring [8].

3 Similarities and Differences Between Wildlife and Human Biobanks

The first fundamental difference between repositories that store human versus wildlife biomaterials is the purpose of use (Table 2). The former almost always is designed to address one or a cluster of human health issues involving diseases or medical conditions. Most repositories of this type are affiliated and/or located within a human hospital. While many are specific for applied function, there also are population-oriented collections that store a broad array of specimen types from diverse

Table 2 Comparison between wild animal species biobanks and human biorepositories

	Wild species biobank	Human biorepository
General purpose and applications	• Multiple, diverse species • Samples collected often opportunistically • Broad applications to basic, veterinary and biomedical research (including comparative biology) • Conservation applications (protection, propagation, monitoring)	• Single species • Samples mostly collected/stored for specific purpose(s) • Targeted, basic and/or applied biomedical research • Specialized clinical applications (e.g., diseases, infertility)
Collection of samples and data	• Systematic sampling during routine health examinations or capture • Institutional Animal Care and Use Committee approval for research sample collection (captive and wild populations) • High potential of post-mortem sampling ('genetic rescue') to collect samples for future use • Collection of comprehensive information about the individual (phenotype) or the habitat	• Sampling mainly based on disease or other medical condition of individuals • Institutional Review Board approval for research sample collection and use • Restricted post-mortem collection and use • Collection of comprehensive information about the individual
Processing and storage of samples and data	• Minimal or no Standard Operating Procedures (SOP) or Quality Assurance/Control (QA/QC) • Cryopreservation methods adapted to each species • No link with genomic data yet • Sample ownership depends on institution • Unrestricted archival biomaterials for future use	• SOPs for each type of tissue, and sample QA/QC systems in place • Secure link between the donor's sample and data plus protected donor rights/ownership (especially when connected to genotypic data) • Sample storage issues after patient's death (destroyed or donated for research)
Access and exchange of samples and data	• Free access to scientists • Material transfer agreements • Formal permits required from Convention of International Trade of Endangered Species (CITES) • Lack of standardization for sample/data access and exchange among biobanks	• Ethical, legal and social implications (ELSI) related to sample transfer and use • De-identification of samples used for research • Access regulated by ELSI and biobank-dependent • Lack of standardization for sample/data access and exchange among biobanks

(continued)

Table 2 (continued)

	Wild species biobank	Human biorepository
Biosafety and biosecurity	• Emphasis on preventing sample contamination during processing and storage • Insufficient attention to the potential of disease transmission from samples	• Emphasis on preventing sample contamination and disease transmission • Emphasis on people safety during sample processing
Financial sustainability	• Funding through universities, museums, zoos, private donors • No monetary value linked to the samples	• Funding through public and private sector sources • Commercial incentive to collect and distribute samples
Examples of societies and consortia fostering communication	• International Society for Biological and Environmental Repositories • Global Genome Biodiversity Network • Frozen Ark	• International Society for Biological and Environmental Repositories • Human Heredity and Health in Africa • Biobanking and Biomolecular Resources Research Infrastructure (Europe)

people for multiple uses, including basic and applied research (e.g., developing biomarkers for diagnosis and monitoring). In contrast, wildlife biobanks are not created and managed for any single purpose. The actual or potential scale of application is much broader and often undefined, and the expectation is that the stored biomaterial will find its most important application in the near or long-term. The stakeholders interested in such banks generally are quite diverse and represent specialists in reproductive biology, fertility, genetic and genomics, biomarkers, veterinary medicine, disease surveillance, pathology and eco-toxicity, among other disciplines (Fig. 2; Table 2). As successful species recovery and management always depend entirely on multiple disciplines coordinated closely together, preserved wildlife biomaterials have the opportunity to contribute to integrated conservation at multiple levels [38]. This includes thinking futuristically, for example, storing tissues immediately post-death, realizing that preserving biological factors and the genome itself may be invaluable for as yet unknown conservation-related purposes. This tactic currently is unacceptable for human biorepositories due to obvious ethical and legal reasons.

While there are functional distinctions, all cryorepositories must emphasize high quality protocols and assurance (Table 2). All samples must be properly collected, processed, labeled and maintained according to best practices in a way that minimizes deterioration over time and protects from physical damage. But safeguarding also extends to essential information on every sample, from point of recovery to background to ultimate use. Both human and non-human biobanks must carefully store not only the samples, but also the related clinical, biological and environmental information (Table 2). Thus, a priority for all specimens, regardless of repository type, is sample registration upon entering and exiting the bank in a computer-based

system that is consistently updated and duplicated. Another commonality is the need for replicate (split) samples stored in separate locations for enhanced security. Although standard for all reputable human biorepositories, this practice appears mostly theoretical for wildlife biobanks, largely due to the resource constraints. Importantly, biomaterials from wild species can be archived for later use long after the animal death, which is not possible for human samples for ethical reasons (depending on the agreement with the patient or family, these biomaterials can be stored anonymously for a future research purpose or destroyed; Table 2).

Wildlife biobanks are far behind human repository counterparts in sample use for gene sequencing to generate knowledge for improving decision-making. Sequencing of the human genome was the catalyst for broad medical applications, including understanding patient health and medical needs by creating individual genetic blueprints. The consistent reduction in cost and advancements in bioinformatics and systems biology have led to data super-abundance, sharing and significant medical discoveries and treatments [23]. Whereas genotype data are derivable now from, for example, a blood sample, particularly powerful is the ability to integrate this information with phenotypic records gleaned from patient interviews, medical histories and physical assessments. This approach has generated massive amounts of information for the researchers and clinicians who need it [14]. The potential for applying similar tactics to wildlife species is enormous. Imagine identifying those genotypes that ensure a species, population or individual are more resistant to a devastating disease or more capable of surviving reintroduction into the wild or less vulnerable to the insidious influences of climate change. These will be game-changing approaches in the field of conservation biology.

Clearly, both the wildlife and human biorepository communities must be responsive to the ethical, legal and social implications (ELSI) pertaining to their existence and operation. Those dealing with humans commonly must address issues of fairness to donations from vulnerable populations, providing informed consent, data disclosure to participants, rights to ownership of intellectual property and the privacy/security of participants (Table 2). Specialists associated with wildlife must address different permission issues, specifically Institutional Care and Use Committee (IACUC) approvals for animal welfare and CITES permits for collection and transport of specimens from rare species. This group has paid little attention to intellectual property, which will be a near-term priority. The wildlife community also needs to begin more sophisticated databases that have meta-information but information is sometimes incomplete or missing because of the lack of standardization between the collecting units. By contrast, both the wild species and human biorepository communities could benefit by more definition and refinement on sample ownership. In human-focused facilities, a specimen may have competing owners, the patient, the collector, the storage unit and/or the scientist analyzing the sample ([16]; Table 2). For biomaterials in a wildlife biobank, ownership has been ‘vague’ at best as these specimens generally are stored for forthcoming potential and often a yet-to-be defined specific purpose or use. However, development of ownership standards needs to be a priority and could benefit from existing living animal models. For example, for conservation breeding, when

Institution A owns one animal (a male) and Institution B owns the other genetically appropriate mate (the female), the strategy is to move (ship) one animal to the location of the other for natural breeding. Generally, the ownership of resulting offspring is rotated between the two cooperating institutions. The same approach could be used when banked sperm (rather than whole animals) are transported for AI; the participating institutions could agree preemptively to offspring ownership, logically using the rotation paradigm. For human biorepositories, complexity can occur when a researcher requests a human specimen for research. Issues related to right to privacy, ownership of specimen and its derived data and extent to which the donor shares in research's results all can arise [16]. No one has yet determined if these same questions are even relevant to wildlife biobanks.

Any repository system, regardless of purpose, requires high quality biosecurity and biosafety. Approaches for wildlife versus human banks are quite different, with the former being mostly focused on the samples themselves, whereas the latter emphasize security and safety of the people processing the samples (Table 2). The specific priority for wildlife specimens is avoiding cross-sample contamination, especially by micro-organisms transmitted among samples or, for example, to the recipients of frozen sperm inseminations or oocyte or embryo transfers [5]. Bacterial and viral corruption of samples was recognized nearly 20 years ago, but the dangers associated with contaminated liquid nitrogen containers and even liquid nitrogen itself were largely dismissed as unimportant [5, 30]. Today, this issue is high priority, not only for wildlife, but obviously agriculture where biospecimens are routinely shipped globally. Among the standard operating procedures for avoiding contamination are a series of preventive measures starting with the collection of the biological material, its processing (washing procedures) and storage (disinfection of containers; [5]). However, many of the risks associated with wild species remain unknown in contrast to the situation for human biorepositories where the issue is similar, but the potential contaminants better understood [5].

Finally, of course, a commonality of all banking initiatives is the financial capacity to sustain the repository forever. Good stewards of every such effort are preoccupied with apprehension of inadequate support and the collection being 'orphaned' or lost at some point. The advantage of human biorepositories is the commercial incentive associated with an enhanced or rescued human condition (Table 2). However, profit-related enticements are illegal for wildlife (including their biomaterials) to prevent trafficking of rare species. Therefore, the support for wildlife biobanks must be based on justifications (as articulated above) for preserving bio- and genetic diversity, analogous to why we would support wild animals and plants in parks, reserves, zoos, aquaria and botanical gardens. Growing international awareness that these samples are a form of national asset or wealth (especially if they or the genes within can be exploited commercially) has produced a culture where national governments are keen to prevent biomaterials exports, even for research. This has created some difficulties for biobanks and museums that either cannot accept samples that do not have appropriate legal provenance or, worse, must discard historical, already in-house samples that lack requisite paperwork.

The upside is that there is a growing realization about the importance of sovereign, self-interests that hopefully will ensure new means of equitable and fair resource protection and use, including building more biobanking capacity in underdeveloped countries.

4 The Need for 'Bridges' Between Wildlife and Human Biobanks, and Other Scientific Disciplines

We believe now is the time for more direct interactions among biobanking programs regardless of focus on humans, agriculture or wildlife. Certainly, specialists storing biomaterials to preserve biodiversity and genetic well-being can benefit from the long experiences of the much larger human and food animal repository communities. We also have argued in other venues the advantages of comparative wildlife studies and the resulting knowledge for improving the human condition [9, 39]. Lessons learned have ranged from innovative direct approaches to storing cells, parts of cells or tissues long-term (i.e., vitrification; membrane biostabilization; germinal vesicle and ovarian/testicular tissue preservation; *in vitro* or *in vivo* development of primitive germ cells) to improved production of animal models useful for addressing insidious human health situations.

A first step to bridge-building always is stronger communication, an approach well-recognized as key to sharing improved standards and practices, consolidated maintenance, compatible databases, personnel interoperability and more detailed policies for accessibility and effective biomaterials use [33]. Interestingly, available biobanking expertise and infrastructure in some regions (i.e., eastern Africa or southeastern Asia) can be more developed for livestock and even wildlife species than for humans, perhaps another incentive for more cross-purpose collaborations. Another means of imparting information (or at least recognizing how similar/diverse our processes are) and working towards best practices is sharing through formal society affiliations. Over the last 10–15 years, there has been a marked increase in establishing professional societies that cater to the multidisciplinary, complex topics influencing the successful collection, storage and use of biomaterials. The International Society for Biological and Environmental Repositories (ISBER), a USA-based association established in 1999, has a broad remit that includes human, animal, plant and microbiological specimens. A sister society, the European, Middle Eastern and African Society for Biopreservation and Biobanking (ESBB) was launched more recently (2010) and serves users in those three regions. While most impetus for forming these societies arose from biomedical and industrial research needs, these associations also attract professionals with primary interests in the biological and environmental sciences [33]. Furthermore, while most formal societal interests focused originally on the technical challenges associated with cryopreservation, priority activities have expanded, especially to sample/data acquisition and management (Table 2).

Attitudes also seem to be evolving as specialists in this field realize the need to work together to brand their science while addressing highest priorities. The President of ISBER recently stated (in emphasizing the growing importance of biobanking) 'We are no longer the housemaid of pathology and taxonomy, and we are not to be swallowed by the diffuse area of -omics science … our strength comes from our ability to develop evidence-based procedures to provide biospecimens for effective research applications. Biobanking is a science on its own'. This position certainly is valid for those of us advancing the combined challenges and benefits of collection, storage and use of wildlife biomaterials. Such an assertion—to think more comparatively, broadly and globally—makes sense because in the end, all animal life (human, food animal, wildlife) is interconnected, and what contributes positively to one could have a constructive influence on others. Collectively then, these overall resources become global biorepositories that are underpinned by a complex, but universal biobanking science all of which are helping to sustain the web of life.

What are fostered, if not formal partnerships, are at least networks that encourage if not ensure high quality standards, improved best practices and better coordinated biomaterials exchange, all in accordance with national and international legislation and treaties. Individual smaller models already are forming. For instance, the Common Biorepository Model (CBM; wiki.nci.nih.gov/display/TBPT/Common + Biorepository + Model + [CBM]) was developed by the National Cancer Institute (NCI) to reduce the time required by researchers to locate both the bank and the specimen needed. A similar approach has been envisioned by the Global Genome Biodiversity Network (GGBN; www.ggbn.org) whose purpose is 'to foster collaborations among repositories of molecular biodiversity in order to ensure quality standards, improve best practices, secure interoperability, and harmonize exchange of material in accordance with national and international legislation and conventions'. Regardless, when creating or expanding any repository, it is prudent to generally 'think bigger' while being more nationalistic or at least regional. There also are no major impediments for why properly designed banks could not manage biomaterials simultaneously from human, food animals and wildlife species. The essential infrastructure, personnel, equipment and basic methodologies are the same or quite similar. A greater operational scale not only reduces unit costs, but, more importantly, allows learning from each other while improving overall value and utility of stored specimens. As one example, the NCI is helping to develop a larger environmental repository in Kazakhstan based on the presence of a smaller cryopreservation facility originally designed for drug discovery and plant storage.

Creating links involves more than simply cross-talk between institutions that are preserving different types of biomaterials. There also is a need to tout the advantages as well as the sophistication of the science to other investigators in related fields, including in species conservation biology.

One priority message is ensuring that non-cryobiologists understand the complexity of this specialized discipline. Living cells and tissues are not 'preserved' by simple placement in a mechanical freezer. Rather there are highly diverse biological traits across species (even within the same taxonomic family; [39]), and this specificity

especially extends to cryo-sensitivity of germplasm, embryos and tissues [8]. For example, spermatozoa and embryos have ideal cryo-requirements (i.e., preferred cryoprotective agent, cooling and thawing rates) that vary with species (or even genotype within species), all of which affects post-thaw survival and the capacity to produce living young. Although we do not yet know the impact of these preemptive storage treatments on emerging biotechnologies related to genomics, transcriptomics and proteomics, it almost is certain that how a specimen is stored influences its ability to be useful for research and applied animal management. And, as it eventually will be possible to derive germ cells and produce embryos from an array of non-reproductive cells (perhaps any cell source), it makes sense that more attention is paid now to identifying the optimal means of preserving all biomaterials. Ensuring cell and tissue recovery along with DNA stability and integrity will maximize what will be a transcendental revolution not only for biomedicine, agriculture and industry, but also for wildlife conservation, evolution and ecology.

5 On the Horizon for Fostering Global, More Effective Biobanking Programs

One means of nurturing development of larger, more all-encompassing biorepositories that include human and animal materials is more innovations in biobanking science. One example is overcoming our near total reliance on cryopreservation—suspending biophysical and biochemical reactions through low temperatures. This approach requires exposing biospecimens to toxic cryoprotectants followed by substantial stresses imposed by osmotic events, freezing and then storage at subzero temperatures in electricity-dependent (−80 °C) freezer units or liquid nitrogen (−196 °C) dewars. These systems are expensive, require intensive management, complex security, ventilation and back-up devices in case of equipment failure. These challenges are significant for developed countries and near unsurpassable in the developing world, which holds most of the rarest biodiversity and where liquid nitrogen itself often is a scarce or unavailable commodity. Likewise, effective cryoprotocols have yet to be developed for many platelets, stem cells, oocytes, algae and fungi, all of which are complex and highly vulnerable to cryoprotectant exposure and chilling/freezing temperatures that cause DNA aberrations and cell/tissue damage and death [1]. Our laboratory is considering lessons that can be learned from what occurs normally in nature to safely, simply and economically preserve biomaterials. For example, spermatozoa of bees, sharks and bats remain viable for up to 12 months in the female's reproductive tract at core body temperatures [17]. Many microorganisms and protostomal animals (i.e., tardigrades) are able to suspend their life cycle during extreme conditions by natural desiccation at ambient (~20 °C) temperature. This 'anhydrobiosis' occurs from an ability to accumulate natural sugars (including the disaccharide trehalose) intracellularly to preserve membrane lipid bilayers and proteins in a stable, glassy, dried state [11].

Knowing that such phenomena occur in nature should be impetus for us to consider the possibility of preserving living biomaterials without the need for extremely cold, injurious temperatures. For example, upon drying, intracellular proteins and macromolecules compensate the loss of hydrogen bonding with water by forming connections with other molecules, thereby, resulting in biostabilization. Recently, it has been shown that extracted human DNA and RNA can be stabilized and maintained using polyols (long-chain sugar alcohols) for 12–45 months at ambient temperature, sufficiently so to allow nucleotide sequencing when convenient [7]. Likewise, it has been demonstrated that compacted sperm DNA retains structural and functional integrity after convective drying and then ambient temperature storage [27]. After rehydration, desiccated mouse spermatozoa injected into oocytes have produced blastocyst-stage embryos that, when transferred to recipients, have resulted in live-born young. In our laboratory, we are exploring the option of not even needing to preserve the entire germ cell. For example, we have demonstrated an ability to remove the germinal vesicle from the cat oocyte, desiccate, store at +4 °C, rehydrate, re-incorporate into a conspecific enucleated oocyte and then inseminate to produce an early stage embryo [13]. Other support for this concept comes from Loi et al. [28] who have recently reviewed that animals and plants undergoing anhydrobiosis are producing late embryogenesis-abundant proteins that confer remarkable tolerance to desiccation. These proteins now are being transfected into human hepatoma cells to engineer biostability for dried state, room temperature storage [26].

Thus, one of the priorities is exploring alternative preservation methods that may well be independent of freezing. Such a discovery would have massive appeal, including for addressing the explosion of new, emerging diagnostic and forensic technologies that allow physicians and conservation specialists to screen hundreds of biomarkers. Such profiling requires the highest quality bio-specimens and the transport of samples quickly and safely using standards that cannot always be met by classical cryopreservation approaches. An effective biostabilization strategy would be a boon to thousands of clinical laboratories, zoos and museums to help alleviate escalating costs associated with conventional cryo-storage. It is estimated that these future sample preservation approaches will require only one tenth of the space needed for −80 °C freezers [29].

A second priority also is related to ‘bigness’, especially the enormous amounts of data being generated by the use of growing collections, especially for the emerging fields of genomics, proteomics and metabolomics [23]. New data processing, analysis and storage systems will be required to manage and integrate biomaterials and massive amounts of generated information. This will be no small challenge as current biobank databases largely have self-served a given collection rather than being linked to the research community [12]. New systems will need to be much more sophisticated and not only connected among the patient, physician and medical outcome, but also, in the case of a rare wild animal, its manager/protector(s), native habitat and conspecifics. While human biobanks will play a more centralized role in medical research and the evolution of ‘precision medicine’, such databases

for wildlife will be invaluable for tracking the well-being of species, for informed conservation decision-making and quick turns in adaptive management.

A final priority is building biobanking personnel capacity. Many of us came into this field serendipitously—our research studies required large-scale collection and storage of biomaterials—and we reacted with minimal knowledge about cryopreservation or collections management. Inevitably, we made significant mistakes and learned valuable lessons, the latter needing to be instilled into the next generation of professionals in the field—in biobanking science. This would be another way by which human and animal repository specialists could collaborate and contribute to a larger goal of protecting and using biomaterials. While short duration training courses are useful, we are proponents of more training at the protracted graduate level. For example, many of our graduate students' thesis projects involve detailed cryobiology and hands-on experiences related to biomaterials management. Certainly, another component to more formalized professional training is capacity building in species-rich, underdeveloped countries, where such investments will pay big dividends in protecting bio- and genetic diversity.

6 Conclusion

While this chapter has documented some distinctive differences between wildlife biobanks and human biorepositories, the overlap in common challenges and needs is significant. For those of us dealing with the collection, storage and use of biomaterials from rare, wild animals, we will continue to learn from our counterparts in human biomedicine. However, we also would challenge these same colleagues to think bigger about enormous opportunities by creating, accessing and sharing biomaterials from much richer, biodiverse, genetically unique resources. After all, data being generated from non-traditional animals (i.e., wildlife) already in fact is benefiting human health [39]. And, we suspect that examples of mutual benefit between conservation biologists and human health specialists will expand exponentially when readily accessible diverse biomaterials are examined using new biotechnologies to unleash massive amounts of untapped information in each sample. New initiatives to develop these more universal, even global biobanks would be a worthy joint endeavor of our respective human health and conservation biology communities. We look forward to advancing this dialogue.

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Index

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