Chapter 6
Biobanking Best Practices and Publication Standards

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Abstract Initially focused primarily on collecting samples for diagnostic purposes in pathology settings, biobanks have evolved into complex organizations engaged in advancing personalized medicine and translational research. This evolution has involved the development of biobanking best practices and the transformation of a field driven by empirical approaches into the emerging area of biospecimen science. It has become increasingly important to develop evidence-based practices for collecting specimens and data which can be shared with confidence with international collaborators. Aside from these technical approaches, other factors play crucial roles, such as developing publication standards; ethical and regulatory issues; business planning and sustainability; and approaches to data collection and sharing.

Keywords Biobanking · Best practices · Publication standards · Biospecimen

6.1 Introduction

Biobanking is often thought of as the simple technical and logistical approaches to collecting, processing, and storing biospecimens ("biospecimens" as used in this chapter includes liquid samples such as blood, urine, saliva, as well as tissue and cellular samples). However, biobanking is a more complex endeavor and is the term which incorporates the physical infrastructure used to house specimens and data systems, as well as the policies and procedures which are developed to govern its operations. And usually one thinks of large warehouses of freezers with frozen blood or tissue samples, or pathology departments with collections of formalin-fixed, paraffin-embedded (FFPE) tissues. Generally, these pathology collections were the most prevalent in the origins of biobanks over 100 years ago [1]. These collections, generally of the FFPE type, were (and still are) necessary for patient diagnoses in clinical centers. Biobanking grew out of the recognition that such collections can also contribute significantly to biomedical research endeavors. Over the

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decades the value of pathology collections to research led to more organized efforts to leverage such diagnostic specimen collections into translational research programs. Biobanking is now considered a cornerstone in the development of personalized (or precision) medicine [2]. The diversity of specimen types collected for such studies has expanded to a variety of tissue, liquid, and cellular samples procured and processed in multiple formats. Some high-profile biobanking failures, and the general sense that biospecimen quality was not adequately controlled, led to the development of best practices, the evolution of biospecimen methods research [3], and generally the recognition that biobanking needed to "come of age" and become a "science" in its own right [4, 5].

In this chapter, the development of biobanking best practices will be discussed, along with the roles of publication standards, and certification and accreditation standards based on best practices.

6.2 Biobanking Best Practices

6.2.1 The Evolution of Biobanking Best Practices

As biobanks became larger and more complex in terms of the numbers and types of specimens and data comprising the collections, a series of high-profile best practices were published. The International Society for Biological and Environmental Repositories (ISBER) published the first edition of its best practices in 2005, followed by three new editions, the latest published in 2018 [6]. Other best practices have been published by the US National Cancer Institute (NCI) [7], International Agency for Research on Cancer (IARC), and the Organisation for Economic Cooperation and Development (OECD). Several reviews have outlined the development of multiple international best practice documents [8, 9]. Generally, biobanking best practices contain documented procedures developed empirically by the larger institutional and commercial biobanks such as shown in Fig. 6.1, which tend to have well-developed quality management, information systems, and specimen handling processes in place. As biobanking has developed into biospecimen science, there has been a trend toward developing evidence-based standard procedures for incorporation into best practices. Engel et al. discuss the NCI's approach to developing such procedures and provide a detailed example for snap freezing of postsurgical tissue specimens [10].

The following shows the major contents headings from the NCI *Best Practices for Biospecimen Resources* [7]:

(a) **Scope, Applicability, and Implementation.**
(b) **Technical and Operational Best Practices**

1. Biospecimen resource management and operations
2. Biospecimen collection, processing, storage, retrieval, and dissemination

Fig. 6.1 US National Cancer Institute Biobank with liquid nitrogen and mechanical freezers. (Photo courtesy of Leidos Biomedical Research, Incorporated)

3. Quality management
4. Biosafety
5. Collecting and managing clinical data
6. Biospecimen resource informatics: data management and inventory control and tracking

(c) **Ethical, Legal, and Policy Best Practices**

1. Principles for responsible custodianship
2. Informed consent
3. Privacy and confidentiality protections
4. Access to biospecimens and data
5. Intellectual property and resource sharing
6. Conflicts of interest

Generally, the technical and operational practices for biobanks have developed to a point where most operations follow similar or identical procedures. Current best practices documents and other publications provide detailed recommendations concerning the standard methods for collection, processing, storage, and shipping of blood, tissue, urine, saliva, and other commonly collected specimens [11–13]. Epidemiologic studies may involve a complex array of sample collections requiring the development of multiple standard operating procedures (SOPs) [14]. Emerging

specimen types and new technologies require regular review and updates to standard practices. As discussed in the section Toward Evidence-Based Practices, there are still many unresolved questions concerning the optimal methods for collecting, processing, and storing specimens, due to the effects of pre-analytical variables and other potential biases.

In terms of ethical, legal, and policy practices, those tend to be more unsettled and controversial (see Section Ethical, Legal, and Social Issues). In addition, such issues are more subject to local and national regulations, making international collaborations more difficult in terms of the exchange of specimens and data [15].

With the proliferation of best practices from a variety of sources, as well as the increasing number and complexity of biobanks, it has become important to ask whether there should be one overarching set of best practices which can be adopted internationally. A review of international biobanking best practices in 2010 listed 14 organizations which had published such documents at that time [16], making for a confusing array of recommendations. This situation is difficult to resolve for the reasons discussed above, making it important to develop and adopt evidence-based practices. ISBER and other international biobanking organizations are engaged in attempting to educate biobanking scientists and move the field toward international coordination and harmonization. One of the more comprehensive efforts, and a good model for the future, is that of the Biobanking and Biomolecular Resources Research Infrastructure (BBMRI), organized and funded by the European Commission [17], which is coordinating efforts in Europe and elsewhere to develop sustainable biobanking programs. BBMRI's initiatives include hosting and participating in biobanking-related workshops and training programs, and developing educational materials which will hopefully result in more international cooperation and coordination [17, 18].

6.3 Evidence-Based Practices and Standards

6.3.1 Specimen Quality Issues

As biospecimen science has developed over the past 10 years its practitioners have learned valuable lessons from some high-profile failures in studies, at least partially due to biospecimen handling and quality issues. As noted by Spruessel et al. [19] in their study of the effects of tissue ischemia duration on gene expression: "While scientists control variables in their experimental settings and try to minimize them as much as possible, they usually barely know about the background of clinical samples."

In the NIH project The Cancer Genome Atlas [20], there were some early specimen quality failures due to retrospective tumor samples procured from existing frozen collections not meeting the pathology or molecular quality standards set for the study [21]. More than half the specimens initially collected for the project failed

quality control. Ultimately the project leadership decided to transition from retrospective specimen collection to prospective collection using carefully controlled standard protocols. This approach led to a quality success rate of over 80%.

In establishing the treatment protocol for potential breast cancer patients, HER2 (human epidermal growth factor 2) assays are performed [22] in order to assess whether treatment with Herceptin will be effective. In 2007, the College of American Pathologists (CAP) [23] and the American Society for Clinical Oncology (ASCO) [24] completed a study of the interlaboratory variability of HER2 assays in a number of clinical laboratories. The study determined that the rates of false positives and false negatives approached 20%. In publishing their findings and recommendations [25, 26] ASCO and CAP reported that at least some of the issues with the HER2 assays originated with variability in the breast specimen fixation methods.

Many other examples of the effects of pre-analytical variables on specimen quality and variability have been published, although as discussed in the following sections, efforts to compile a comprehensive literature concerning biospecimen science are fairly recent developments. For examples of such studies, see papers by Koury et al. [27], "Delay to formalin fixation effect on breast biomarkers" and Hewitt et al. [28], "Impact of preanalytic factors on the design and application of integral biomarkers for directing patient therapy." Poste [29], in "Biospecimens, biomarkers, and burgeoning data: the imperative for more rigorous research standards," emphasizes the importance of developing approaches to mitigate the effects of biospecimen pre-analytical variables. Ransohoff and Gourlay [30] discuss the sources of bias in biomarker studies, which can involve the effects of specimen handling. In addition to the pre-analytical variables, such effects can include batch effects in analyzing samples and differences in the sources of samples, for example, among cases and controls (Table 6.1).

6.3.2 Quality Management Systems

As biobanking best practices have developed, and biospecimen science has emerged in the wake of the issues discussed in the last section, the development of quality management systems (QMS) has become a major focus in the "professionalization" of biobanks. In general terms, biobanks have adopted the quality assurance (QA) and quality control (QC) practices long utilized in clinical chemistry laboratories, with additional practices developed which are unique to biobanks [31, 32].

Basic QMS for biobanks requires SOPs for each function of the operation [33–36]. Staff should be trained in the SOPs and procedures should be in place for periodic review, and an electronic document control system should be in place. The basics of quality management are described in detail in the current major best practices editions from ISBER, NCI, OECD, and other organizations [16].

As biobanking and biospecimen science have evolved, so have quality management systems. The early adopters of more comprehensive QMS were biobanks which collected and stored biospecimens for clinical applications and were subject

Table 6.1 Adapted from Ransohoff and Gourlay, J. Clin Oncol 2010 [30]

Source of bias	Location of bias: before or after specimens are received in the laboratory Before After	Example
Features of subjects, Determined in selection: Age Sex Comorbid conditions Medications	X	Cancer subjects are male, whereas control subjects are mainly female Bias: Assay results may depend on sex
Specimen collection	X	Cancer specimens come from one clinic, whereas control specimens come from a different clinic Bias: Assay results may depend on conditions that differ between clinics
Specimen storage and handling	X X	Cancer specimens are stored for 10 years because it takes longer to collect them, whereas control specimens are collected and stored over 1 year Bias: Assay results may vary with duration of storage, or with different numbers of thaw-freeze cycles
Specimen analysis	X	Cancer specimens are run on 1 day, whereas control specimens are run on a different day Bias: Assay results may depend on day of analysis in a machine that "wanders" over time

Note: The table shows examples of different sources of bias and the location of the bias before or after specimens are received in the laboratory. The list is not exhaustive; other biases may be important, and the biases listed may or may not be important in any given research study, depending on details of biology and technology (i.e., what is being measured and how it might be influenced)

to FDA inspection. These operations developed QMS based on Good Manufacturing Practices (cGMP) [37]. cGMP involves adhering to strict standards in terms of SOPs; security; detailed documentation of equipment installation; performance and maintenance; IT systems; and a thoroughly documented chain of custody for all samples and reagents. More recently some biobanks, in particular those which engage in international collaborations, have undergone the certification process of the International Organization for Standardization (ISO) [38]. The ISO standard which is generally adopted for biobanks is ISO 9001 [39]. However, ISO 9001 was developed for general quality management purposes, and not specifically for biobanking operations. A more biobank-specific ISO standard (ISO 20387) was developed by an international committee with experts from ISBER and other organizations and published in 2018 [40]. Any ISO certification process is comprehensive and

successful completion of the application provides assurance that the organization is committed to meeting high-quality management standards.

6.3.3 Evidence-Based Methods

Although the recognition of the role of quality management was an important development in biobanking, issues concerning uneven quality of biospecimens remain a major obstacle to the generation of reliable analytical results [21]. Through a number of challenges due to specimen quality issues, as described above, the development of evidence-based procedures has become a priority for many biobanks. The ISBER Best Practices recommend pilot studies to optimize specimen collection and processing procedures [6]. However, often such biospecimen methodology studies are developed only for local biobank or laboratory use and are not widely disseminated or published [4, 5, 41]. The approach which should be taken to develop a new biobanking effort is exemplified by the UK Biobank [42, 43]. In 2008, the project leadership published a series of articles in the *International Journal of Epidemiology* which detailed the preliminary methods studies performed to establish the optimal approaches to collecting specimens for the project, which ultimately included 500,000 participants. The methods studies included assessments of the stability of blood and analytes, automated sample processing, and a novel automated blood fractionation system [44].

Starting in 2008 organizations such as the US NCI Biospecimen Research Network [45] and SPIDIA (Standardization and improvement of generic pre-analytical tools and procedures for in vitro diagnostics [46]) began to take a more organized approach to study the effects of pre-analytical variables and other factors on the quality of specimens and the reliability of downstream analyses [45, 47]. Depending on the analyses to be performed pre-analytical variables may include freeze-thaw cycles for frozen specimens, time intervals from sample collection to stabilization, drugs taken by surgical patients, and other factors [19].

Both the BRN and SPIDIA have published results of their studies [48, 49]. In addition, the NCI maintains the Biospecimen Research Database (BRD) [45], which is a compilation of summaries and conclusions from over 2000 biospecimen research papers from dozens of journals. Figure 6.2 shows the BRD's approach to searching for papers according to the stage of the "biospecimen life cycle," integrated with examples of potential pre-analytical variables which may affect specimen quality and analytical results.

Since biospecimen science involves multiple scientific disciplines, such publications are found in clinical chemistry, pathology, epidemiology, genomics, proteomics, and many other journals devoted to basic, translational and clinical research. NCI investigators from the Biorepository and Biospecimen Research Branch (BBRB) have published reviews on topics extracted from BRD papers [10] as an approach to expand the literature on evidence-based biobanking practices. An example of a paper concerning how pre-analytical variables can affect urine

Fig. 6.2 The NCI Biospecimen Research Database search categories, showing stages of specimen acquisition, processing and storage, and potential pre-analytical variables (factors)

collected for metabolomics studies, curated and summarized in the BRD, is shown in Fig. 6.3. However, the literature concerning the effects of pre-analytical variables and other factors which may affect specimen quality is often conflicting. Additional comprehensive efforts will be needed to arrive at evidence-based standards which are widely adopted in the basic and clinical research settings. The conflicting data in the literature and economic factors continue to be obstacles to the adoption of new biospecimen collection and processing standards.

6.3.4 Publication Standards

Another issue which is an obstacle to the development of evidence-based biobanking standard procedures is the general lack of rigor in reporting specimen collection, processing and storage conditions, and other sample handling details in manuscripts. This issue is made even more difficult to resolve due to the multiple scientific disciplines which are involved in biospecimen-related research. As already noted, articles from studies which involve significant collection and use of specimens may appear in journals which focus on pathology, epidemiology, genomics, proteomics, clinical chemistry, and other areas of research. During the past 10 years, several sets of standards have been published which encourage publishers, authors, editors, and reviewers of manuscripts to ensure inclusion of sufficient details about specimen collection and handling, in order for the validity of the results to be evaluated. The REMARK guidelines [50, 51] were developed primarily to guide investigators in reporting standards for biomarker discovery and development but included several recommendations concerning specimen handling. More recently, an international committee of experts led by the NCI BBRB, developed Biospecimen Reporting for Improved Study Quality (BRISQ) [52, 53]. BRISQ is a set of standards which is designed to encourage authors to include a standard list of specimen variables in their manuscripts' materials and methods. BRISQ variables are organized into three Tiers according to a set of priorities and consideration of the complexity of collection of the information. BRISQ Tier 1 includes the items which are most important to report and should be readily available to investigators, such as

Standard operating procedures for pre-analytical handling of blood and urine for metabolomic studies and biobanks.

Author(s): Bernini P, Bertini I, Luchinat C, Nincheri P, Staderini S, Turano P

Publication: *J Biomol NMR*, 2011, Vol. 49, Page 231-43

PubMed

Found in 1 study(s)

Study Purpose:

The purpose of this study was to determine the effects of centrifugation speed (450 x g, 1000 x g, 3000 x g, or 11000 x g), filtering or adding sodium azide to centrifuged or uncentrifuged specimens, frozen storage temperature, and storage of preserved or unpreserved specimens at -80 degrees C and subsequently at room temperature on NMR profiles. Urine from 2 individuals was aliquoted, centrifuged for 5 min at 4 degrees C or left uncentrifuged, subjected to various pretreatments (filtration, enzymatic inhibitors, sodium azide or none), frozen for 1 week or used fresh, and stored for up to 24 h at room temperature.

Specimens: Fluid - Urine ***Preservation Types:*** Frozen, Other Preservative, None (Fresh) ***Diagnoses:*** Not specified

Platforms:

Small molecule - NMR

Carbohydrate - NMR

Summary of Findings:

The difference between the first component of the spectra from the centrifuged and uncentrifuged specimens was greatest when the centrifugation speed was 1,000 or 3,000 relative centrifugal force (RCF). NMR spectra from specimens centrifuged at 11,000 RCF were closer to those in the specimens that were uncentrifuged, which the authors attribute to breaking down of the cells. The effect of centrifugation speeds was more pronounced in urine with a high cellular content. When urine was centrifuged prior to frozen storage for a week, the NMR profile was different from that when specimens were not centrifuged prior to frozen storage, but the magnitude of the difference was greater when the specimens were stored at -80 degrees C rather than in liquid nitrogen (8% as much change) or when NMR profiles from fresh centrifuged and uncentrifuged urine were compared (9% as much change). Importantly, changes observed after freezing or centrifugation were very small compared to the interindividual variability. Fresh or previously frozen, but unpreserved urine stored for 24 h at room temperature showed a spectral shift in pH sensitive metabolites as the specimen became more alkaline. Importantly, with storage at room temperature, succinate and acetate increased while urea, lactate, and glutamate decreased. However, specimens that were centrifuged and filtered showed fewer changes in spectra with storage at room temperature than specimens that were preserved with sodium azide, those that were unpreserved, or those only centrifuged prior to analysis or storage at -80 degrees C. When urine was stored for 24 h in an inert atmosphere rather than the normal atmosphere, the only difference was a slight reduction in the change in succinate. Addition of acetohydroxamic acid inhibited the decrease in urea with storage, and addition of EDTA at least partially attenuated the change in succinate and urea with storage.

Fig. 6.3 Example of a paper curated and summarized in the NCI Biospecimen Research Database. (From [45])

sample type; collection method; stabilization method; storage temperature and duration; shipping temperature. Tier 2 includes items which may be important pre-analytical variables for some analyses and should be reported if available, such as time intervals between collection and stabilization of the specimens, and time the samples remain in fixative. Tier 3 includes items which may be less commonly recorded such as the number of times a sample has been thawed and refrozen; details of sample shipping; time from cessation of blood flow to biospecimen excision (warm ischemic time). Both REMARK and BRISQ were published simultaneously in several journals, and their implementation has been endorsed by multiple journals.

A newer specimen collection documentation scheme is the **S**tandard **PRE**-analytical **C**ode (SPREC) [54–56], which involves applying a standard set of codes to a specimen collection procedure. An example is (quoting from [56]):

> Solid tissue or cytologic specimen **TIS-BPS-N-B-RNL-A-A**. This corresponds to a solid tissue (TIS) specimen that has been collected as a biopsy (BPS), with no warm ischemia (N), with cold ischemia of <10 min (B), fixed in RNALater (RNL) for <15 min (A) and stored in a 0.5- to 2 mL polypropylene tube at a temperature between −85 and −60 °C (A). Biopsies, obtained either at time of traditional surgery, laparoscopy, or puncture, and cytologic specimens such as fine needle aspirates, are assigned the same SPREC.

All of these initiatives concerning quality management, biospecimen methodology research, the development of evidence-based practices, and reporting standards are significant advances in biobanking. However, such initiatives will only be effective if evidence-based standards are incorporated into biobanking best practices and widely adopted. That has yet to happen.

6.4 Conclusion

Biobanks have evolved from collections of specimens where collection, processing, and storage were not well-controlled into a branch of science for which there are professional organizations, best practices, and international collaborations involving complex logistics and regulations.

The empirical biobanking practices of the past are giving way to careful consideration of pre-analytical variables which affect specimen quality, and the development of evidence-based practices.

Quality management systems and more highly trained technical staff have led to the "professionalization" of biobanking. Recognition of the importance of publishing biospecimen science articles has led to the development of multiple reporting guidelines such as BRISQ and SPREC.

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