Chapter 11
The Future of Biobanking: Meeting Tomorrow's Challenges

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Abstract Biobanking has traditionally encompassed the collection, processing, and storage of biological samples and other specimens from environmental sources. Most of the procedures currently used by biobanks have involved processing tissue and blood samples. Formalin-fixation of tissue samples and storage at ambient temperature, and freezing blood fractions are the normal methodologies. However, recent developments in biospecimen management promise to revolutionize biobanking. Economic pressures have resulted in new storage technologies, including dry storage, which promise to reduce the high cost of freezer storage. New analysis platforms including genome-wide association studies and metabolomics have altered biospecimen processing schemes. Sample types have evolved to include circulating tumor cells and induced pluripotent stem cells. These developments will lead to the need for additional methods to assure their proper processing and storage for translational research studies. As these new developments evolve and international collaborations continue to grow, there will be an additional need to coordinate best practices and continue to perform biospecimen methods research to develop evidence-based practices. In addition to technical aspects, there are serious ethical and regulatory concerns that will require additional guidance, including consideration of issues around the return of research results to biospecimen donors, and reporting incidental clinical findings.

Keywords Biobanking · Biorepository · Biospecimen · Biospecimen research · Circulating tumor cells · Induced pluripotent stem cells

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11.1 Introduction

Various aspects of the future of biobanking have been highlighted and discussed in other chapters in this volume. In this chapter, we will bring together those concepts and discuss the major initiatives that we believe will comprise the future of biobanking and the challenges that will need to be overcome to realize the full potential of biobanking to support and transform the biomedical research infrastructure.

First, it needs to be reiterated that even the definition of biobanking is somewhat controversial [1], which complicates the discussion of its future directions and challenges. In addition, there are several types of biobanks including clinical or hospital-based and epidemiologic, as well as various types of basic and translational research biobanks. Biobanks can also hold collections of environmental samples. However, for the purposes of this volume, we have concentrated primarily on issues related to the major types of human biospecimen biobanks. The future of biobanking in this context will depend on consideration of several technological, ethical/regulatory, and other factors outlined in this chapter. Already, over the past 10 years, we have seen steady progress in the development of biobanks beyond the traditional model of freezing samples from pathology collections and research laboratories, with little consideration of the variables that can affect their stability and long-term utility. As the field develops more quickly in coming years, change will occur at a much faster pace. We are already, for example, seeing that the evolution of "-omics" including genomics, proteomics, metabolomics, transcriptomics are having significant effects on the technical, ethical/regulatory, and economics aspects of biobanking [2].

11.2 Future Technical Developments and Challenges

The evolution of biobanking as a recognized branch of scientific research [2, 3] has resulted in the recognition that, like other branches of science, biobanking requires an organized approach to developing and implementing technological developments. Traditionally two major approaches to biospecimen banking have been followed: formalin fixation and paraffin embedding (FFPE) in pathology laboratories; and freezing various liquid (blood, blood fractions, urine, saliva, etc.) and tissue samples for epidemiologic studies. Future technical developments will need to consider the aspects discussed below.

11.3 Biobanking Infrastructure

For many years the "infrastructure" of biobanks was mainly based on pathology collections of FFPE samples and frozen collections of tissue and liquid biospecimens. Although these biobanks could be large "freezer farms" or smaller collections

within pathology departments or research laboratories, these models rarely varied from a technological viewpoint.

These traditional models are now changing and will continue to evolve. The most obvious of these trends is that the large freezer-based biobanks are recognizing that from scientific, logistical, and economic viewpoints, newer ways to process and store samples need to be developed. Two major advances are facilitating this trend: development of "dry storage" techniques that provide stable biospecimens of adequate quality for most analyses [4]; and alternatives to FFPE samples that are recognized by pathologists to be of similar or superior quality, such as PaxGene Tissue [5].

The future of such developments will depend on further biospecimen research to validate the long-term stability of samples processed and stored using these new processes. In addition, such advances will continue to evolve as different and smaller sample types are introduced into the biobanking realm, as discussed in the following sections.

11.3.1 Sample Types

Tissue, tissue microarrays, blood, urine, and saliva have been the typical specimens collected for clinical, basic, epidemiologic, and translational research studies. Newer specimen types include induced pluripotent stem (iPS) cells [6] and circulating tumor cells (CTCs) [7]. iPS cells, CTCs, and other single cell types are becoming significant tools for biomarker discovery and development as well as drug development and other biobanking-related applications. As these various new sample types are developed as research tools, biospecimen science principles will need to be applied as for all sample types, i.e., the optimization of collection, processing, and storage parameters. Pre-analytical variables will as for all specimen types be important to sort out.

In terms of sample types, see the review by Cole et al. [8] concerning trends in specimen use for cancer research. Overall there has been a trend toward the use of RNA-based samples and analytical techniques.

11.3.2 Sample Analyses

Genome-wide association studies, next-generation sequencing, and advances in proteomic analyses are among the analytical platforms that have revolutionized various research endeavors. What sample types and volumes/sizes will be necessary for newer analytical techniques, and what biospecimen research gap analyses and studies will be required as additional advances in analytic technologies occur?

11.4 Best Practices

As noted in Chap. 6, 2nd Edition a variety of biobanking best practices and guidelines have been developed over the past 10–15 years [9]. Although these documents have a number of common themes and agree in general on many of the technical and ethical/regulatory aspects of biospecimen collection and management, there are some significant differences. Most of these differences relate to national and international variations in the implementation of informed consent and other regulatory procedures. But overall there are two major problems with current biobanking best practices: the lack of research that results in evidence-based rather than empirical practices; and the lack of international cooperation and harmonization of practices.

Major organizations such as the International Society for Biological and Environmental Repositories (ISBER), the US National Cancer Institute (NCI), the European, Middle Eastern and African Society for Biopreservation and Biobanking (ESBB), the Organisation for Economic Cooperation and Development (OECD), the standardisation and improvement of pre-analytical procedures for in-vitro diagnostics project (SPIDIA), and the Biobanking and Biomolecular Research Infrastructure (BBMRI) have made significant contributions to the development and implementation of biobanking best practices [10, 11]. The early versions of these documents, particularly the technical aspects, were based on the experiences of early biobanking efforts and empirical evidence that particular practices led to longer term stability and quality of biospecimens. In terms of the ethical, legal, and social issues (ELSI), biobanking best practices have evolved from national and international standards and regulations that were develop based on the Helsinki and United Nations recommendations [12]. However, as biospecimen research has developed, it is now recognized that the future success of biobanking will depend on evidence-based practices [13]. This is a particularly important point since biomedical research, in general, is now and will continue to be more collaborative and international in nature. As more such collaborations evolve into biobanking networks it is important that consistent standards are developed to assure the consistent quality of biospecimens. In turn, consistent quality requires the consistent application of evidence-based best practices. And evidence-based practices will require more biospecimen research that is published in peer-reviewed journals, and constantly updated and reviewed to arrive at consensus opinions on the implementation of changes in biobanking practice. The US NCI Biospecimen Research Database [14] as well as ISBER's efforts in documenting biospecimen research publications, need to continue and expand to support the development and documentation of evidence-based practices [15]. This is not a trivial undertaking and will require the involvement of international organizations and biobanking experts.

A second aspect of the international cooperation and harmonization noted above is the need to better control the development and implementation of best practices, in order to provide new and developing biobanks and networks with consistent standards to follow. Currently, it is still the case that new biobanks and biobank networks tend to "reinvent the wheel" in at least some aspects of their planning and

implementation. Often these missteps revolve around such critical issues as the design of information systems and informed consent processes that have not considered well-established approaches thus wasting valuable time and resources. The future development of successful biobanking efforts will depend on better international coordination of best practices. Organizations such as ISBER, ESBB, and BBMRI will need to take the lead in coordinating such efforts, especially as significant new biobanking efforts are being developed in, for example, China, India, and Africa [16].

11.5 Information Technology

Information technology (IT) advancements continue to provide new tools that assist in the necessary functions of tracking steps involved in collecting, processing, storing, and disseminating specimens, as well as linking analytical platforms with specimen data. Some of the issues that remain to be resolved are generally all in the area of agreeing on common best practices to allow the convenient exchange of data. "Big data" and the expanded use of electronic medical records will also become factors in the collection and analysis of biospecimen-related data.

Other issues that continue to be of concern and will need to be resolved in the next generation of biobanks:

- A consistent approach to developing common sets of minimal clinical data.
- Agreement on IT standards for biobanks, e.g., inventory, tracking, data collection and processing, electronic data collection.
- Better approaches to interoperability of IT systems and efficient exchange of data within biobanking networks and collaborations.
- Related IT issues in molecular epidemiology studies such as batch effects and statistical treatments with respect to various analytical platforms.

11.5.1 Web Resources

More international cooperation will be necessary to provide biobank and sample "locators," i.e., identify existing websites and promote international cooperation. As more studies involving biospecimens develop into networks and international collaborations, it has become more critical to identify methods to locate and obtain access to specimens and data, i.e., when allowable according to local and national rules and regulations and access requirements. Many such locators are available on the Internet, but a way to consolidate and provide access in a convenient way to international users is missing. ISBER created a working group specifically for this purpose [17] that will hopefully lead to improvement in the situation.

11.5.2 Sample Transport and Packaging

Over the past 15–20 years bar coding of samples has revolutionized biospecimen handling by speeding up all processes and reducing errors [18]. The transition from standard one-dimensional bar coding to two-dimensional symbologies such as Data Matrix was especially significant in that smaller codes and labels with more information could be used on the standard storage vials. Now additional advances are allowing RFID codes to gain widespread use in biobanks, with wireless tracking of samples and freezer function [19]. These efficiencies, when combined with advances in biobank automation (see Chap. 3, 2nd Edition), will provide for further cost savings and return on investment.

11.6 Ethical/Regulatory

Ethical, social, and legal issues (ELSI, see Chap. 7, 2nd Edition) are the most difficult to coordinate and standardize, i.e., when compared with the more straightforward and increasingly evidence-based technical biobanking issues. Below some of the issues that will be most challenging to resolve are outlined.

11.6.1 Return of Research Results and Reporting Incidental Findings

Patients and other biospecimen donors are increasingly asking for access to their clinical results. The role of biobanks and their associated laboratories in producing both clinical and research results means that the lines between the two are often blurred. Research investigators have been traditionally been reluctant to share their findings with specimen donors due to the preliminary nature of the results, and the uncertainty of the ultimate clinical utility of the findings. However, this scenario is likely to change in future biobank-supported studies.

Similarly, reporting incidental findings to biospecimen donors who may have not been diagnosed with such a disease, or had been seen for a different reason, is also becoming a point of discussion [20], due again to the blurred line between clinical and basic research studies. Samples may have been collected and examined by a pathologist for the initial diagnostic purposes, but then checked again by a separate pathologist for quality control for a research study. The question will be, as this discussion progresses, how to control the reporting of new incidental findings back to the original clinical team and patient.

11.6.2 International Collaboration

National and international biobanking networks and other international collaborations involving biospecimens have been discussed with respect to adoption of best practices and other standards in several parts of this volume. The scientific issues can be resolved with more consistent adoption of evidence-based practices. However, there are additional issues related to restrictions imposed in some countries concerning the export of biospecimens. It would be advantageous to international collaborations to establish more consistent access policies across international borders.

11.6.3 Informed Consent and Privacy

Many of the issues related to informed consent and privacy related to differences within and among countries concerning their application of local rules and regulations. Such rules and regulations are constantly changing and hinder international cooperation and coordination. In terms of more recent developments to accommodate the return of results, commercial use of samples, and privacy concerns due to new technologies, informed consent documents have been required to evolve to assure that specimen donors are fully informed of all eventualities concerning the use of their samples. In many instances, these concerns are also addressed in a more legal framework in material transfer agreements. However, again, the policies and procedures relative to these issues will continue to be challenging for international collaborations.

In terms of streamlining the consent process, CTRNet in conjunction with the University of British Columbia is developing a "permission to contact" protocol, in which potential biospecimen donors are informed about the potential for participating in research studies early in the process and asked for their permission to contact about such participation.

11.7 Other Issues

11.7.1 Economic Issues and Sustainability

See Chap. 3, 1st Edition for discussion of biobanking economics and sustainability. A future trend will be toward more formal business planning for biobanks, to meet ongoing funding challenges in research.

11.7.2 Biobank Networks

With the emergence in Europe, Asia, Australia, and more recently in Africa of major centers for biobanking networks and national coordination, can these trends be leveraged to promote more international cooperation and coordination? It is critical that as new biobanks are developed in emerging countries, they take advantage of the known best practices and avoid the pitfalls that tend to delay and reduce the efficiency and effectiveness of such efforts. See, for example, the review of challenges faced in the new H3Africa initiative [16].

11.7.3 Educating the Public

In countries where national networks rely on public funding and support, it is vital that biobanking initiatives be fully explained in terms that are understandable to the general public. Potential donors are generally supportive of biobanking when fully informed, but biobanking is not well understood by most of the public, so such informational initiatives need to become more prevalent. See [16, 21, 22] for a discussion of such efforts.

11.7.4 Publications

Publication of biobanking efforts such as the development of evidence-based practices has become more prevalent as biospecimen science has developed. However, the details concerning biospecimen management are typically not well-described in the peer-reviewed literature [23]. It is important that authors, editors, and publishers adopt standards for writing manuscripts with biospecimens as a major component. The Biospecimen Reporting for Improved Specimen Quality (BRISQ) and the REporting recommendations for tumor MARKer prognostic studies (REMARK) guidelines are examples of publication guidelines that are becoming widely adopted [24, 25]. BRISQ will need to become more widely adopted and modified over time in terms of the requirements for biospecimen handling details.

In general, it will continue to be important to promote the publication of biospecimen research articles to advance the field. Such articles tend to be published in a variety of journals including those devoted to clinical chemistry, epidemiology, and pathology. The NCI Biospecimen Research Database [14] is one important central resource for biospecimen research publications and includes search functions that allow the literature to be scanned for important biospecimen pre-analytical variables and other factors. Several meta-analyses have been published which summarize some of the major tendencies concerning such factors [13].

11.7.5 Education

Biobanking education and in general the "professionalization" of the field have gained momentum over the past decade. Several degree programs in biological resource management are in place, including at Catholic University Lyon and in other locales [26]. In addition, online tools are becoming available which allow biobanks to develop and manage their programs with advice developed by experts. Among these are ISBER's Biobank Assessment Tool [27] and the Biobank Resource Centre [28] web resource developed by the University of British Columbia and the (Canadian Tissue Repository Network (CTRNet) [29] allow biobanks to gather information to establish and operate a biobank. Such resources will be critical as biobanking continues to develop as a scientific endeavor.

11.8 Emerging Biobanking Markets and Technologies

In the April 2021 issue of *Biopreservation and Biobanking,* a new section was introduced: Emerging Markets and Technologies. As noted in the Editorial by Gupta and Brooks [30]:

> We are now in an era that was once thought of as science fiction. Although biobanks are often associated with research, the application and concepts stemming from this sector have fueled a new generation of technologies geared at providing direct-to-consumer solutions in emerging markets across the globe. Examples include services to help you better understand your wellness, personalized biome products, targeted marketing campaigns, new data security infrastructure, and much more. This section will highlight the emergence of new markets and technologies that are either adopting or disrupting the biobank framework as they imprint on society. The solutions presented here are anticipated to help drive innovation within the biobank community.

11.9 Summary and Conclusion

In this chapter, we have discussed the questions that will drive the future direction and challenges for biobanking. Throughout this volume, we have tried to identify trends that will influence these directions and challenges. For decades biobanking has been a more or less stable set of practices involving fixed or frozen tissues and blood-derived samples. However, the last decade has seen significant changes in biobanking practices and standards. Many of these changes have evolved from the increasing need for national and international collaboration in translational research studies involving biospecimens. The need for adherence to best practices, as well as the evolution of increasingly sensitive analytical techniques, have also contributed to the critical need to treat biobanking and biospecimen science as full partners in scientific endeavors. As biobanking continues to change in the twenty-first century

it is even more critical to pay close attention to developing and publishing policies and procedures that will lead to a more complete compilation of evidence-based best practices. International organizations such as ISBER, BBMRI, ESBB, and others will be critical partners in this venture.

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