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Invited critical review

The evolution of biobanking best practices

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ABSTRACT

Biobanks and biospecimens are critical components for many areas of clinical and basic research. The quality of biospecimens and associated data must be consistent and collected according to standardized methods in order to prevent spurious analytical results that can lead to artifacts being interpreted as valid findings. A number of international institutions have taken the initiative to develop and publish best practices, which include technical recommendations for handling biospecimens as well as recommendations for ethical and regulatory practices in biobanking. These sources of guidance have been useful in raising the overall consistency and quality of research involving biospecimens. However, the lack of international harmonization, uneven adoption, and insufficient oversight of best practices are preventing further improvements in biospecimen quality and coordination among collaborators and biobanking networks. In contrast to the more straightforward technical and management issues, ethical and regulatory practices often involve issues that are more controversial and difficult to standardize.

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Contents

1. Introduction

Each year, millions of biospecimens are collected for a variety of purposes, including basic research studies, clinical trials, and epidemiology

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studies [1]. Biospecimens are stored in biobanks, which may also be referred to as biorepositories, biospecimen resources, or biological resource centers, for future analysis. In the clinical laboratory setting blood and urine from patients are the basis of most tests and assays [2]. Frozen or formalin-fixed tissues are also collected in clinical settings and used for both diagnostic and research purposes [3]. Standard operating procedures, reference standards and quality control have been basic requirements for clinical laboratories for many years. The American Association for Clinical Chemistry, Clinical Laboratory Standards Institute, the College of American Pathologists and other organizations have been at the forefront in promoting high standards and best practices in the collection, processing and storage of biospecimens for clinical applications. However this has not always been the case for biospecimens collected for research purposes. In recent years a number of organizations have undertaken the development of a series of best practices publications that provide guiding principles for biospecimen resources [4]. These documents cover the technical aspects of biospecimen management, such as collection, processing, storage, quality management, data collection/informatics, as well as ethical and regulatory issues such as informed consent, patient privacy and intellectual property.

In this review we highlight some of the issues that led to the critical need for best practices, how those practices have resulted in a better understanding of the need for international cooperation as global needs for high-quality biospecimens expand, and challenges that lie ahead for implementation.

2. Why do we need best practices?

2.1. History of problems

A variety of pre-analytical factors contribute to poor biospecimen quality, including the use of inadequate or inconsistent collection, shipping, and processing protocols [5,6]. High-profile cases involving invalid proteomic analyses and HER2 [7] clinical assay results due to preanalytical variables not being properly controlled are examples of how the use of biospecimens of poor or unknown quality can be harmful. Too often these issues were not discovered until large numbers of clinical assays were performed or study reports were already released.

2.2. Global nature of collaborations

Over the past 10 years international collaborations have expanded and the necessity to collect and disseminate samples across borders has increased dramatically [8]. For studies where biospecimens are being shared among laboratories and clinics, it is particularly important that samples are of consistent known quality. Since shipping logistics can result in additional specimen quality issues for such collaborations, it is important to plan those details carefully [9]. A number of international networks are coordinating their biospecimen collections through development of common standard operating procedures, compatible informatics systems and harmonized informed consent and material transfer policies and procedures [8]. Examples are the European Prospective Investigation into Cancer (EPIC) study coordinated from the International Agency for Research on Cancer, and the Telethon Network of Genetic Biobanks in Italy [10,11].

2.3. Economics of poor practices

Often the initial reaction to the development and enforcement of biobanking best practices is that they will be too costly due to the need for additional personnel and equipment. For example, one common best practice is the requirement for a freezer alarm system that is monitored 24 hours per day in the event of significant temperature increases or inadequate liquid nitrogen levels [9, Section B.2.6]. For a small repository with one or two freezers this requirement may not be economically feasible. Although case studies are needed to quantify the costs of implementing best practices as well as the resulting benefits, comprehensive economic analyses have not been done. The National Cancer Institute has published preliminary findings and estimates concerning "biobankonomics," which provides a starting point for such analyses [12,13]. An economic benefit that is easy to understand: if samples of inconsistent quality are used for a study and certain analyses have to be repeated with new samples, then funding and other resources have been wasted.

3. Technical best practices

Technical best practices include recommendations for the "basics" of biobanking: collection, processing, storage and dissemination of biospecimens, as well related data collection and management issues. To date most such practices have been based on the long-term experiences of large commercial and academic operations. Most "best practices" are based on laboratory and biobank procedures developed for an institution's or investigator's purposes. Although such procedures may be widely adopted and incorporated into best practices they are often empirical and not published in the peer-reviewed literature. More recently a new field of biospecimen science has emerged that has resulted in efforts to develop evidence-based best practices and standard operating procedures [14]. When biospecimen methods and other research efforts are published they appear in a wide range of journals and are difficult to locate. *Clinica Chimica Acta* and other clinical chemistry, epidemiology and pathology journals are among those publishing significant numbers of biospecimen research papers among the more than 1100 in the NCI's Biospecimen Research Database [15]. As biospecimen research has developed as a field it is becoming more feasible to develop best practices based on evidence from the literature. For example evidence is building that the amount of time that elapses between collecting blood or tissue specimens can affect downstream analyses [16]. Thawing and refreezing blood samples multiple times may also be detrimental to certain analytical applications, although for nucleic acids and certain hormones and micronutrients these effects may be minimal [17]. As these evidence-based practices are introduced into best practices documents, procedures must be in place for periodic expert review of the literature and updates in order for the latest guidance to be included in the recommendations.

3.1. Collection, processing and storage guidelines

To those not familiar with the day-to-day operation of a biobank it may seem a simple matter to collect thousands of samples and properly store them. However even the smallest single-freezer operation in a clinical or research laboratory must have standard procedures for collecting, processing and storing samples.

Examples of variables that must be considered are:

- Blood collection — collection tube additives such as EDTA and heparin can affect analyses [18].
- Storage — for long-term cell viability, storage at liquid nitrogen temperatures is preferable. Other specimens such as DNA and plasma will be stable for most analyses when stored in −80 °C freezers or higher temperatures [9, Section B.2.6].
- Processing —formalin fixation times vary widely among pathology laboratories and may affect downstream analyses [19].

These and other important recommendations are included in all biospecimen best practices documents. Generally the International Society for Biological and Environmental Repositories (ISBER) [20] and NCI practices [9] include comprehensive recommendations. Additional best practices that should be consulted as applicable are those from biobanks in various international locations where recommendations

may be adapted according to local biospecimen needs and uses, and regulatory considerations [4].

3.2. Biobank management practices

Smaller biobanks that are part of larger programs or departments will generally not have a formal management structure except as it exists within the larger organization. However management and operational structures are important for larger academic, government and commercial biobanks. These practices usually include a management and staffing plan; roles and responsibilities for all personnel; oversight committees that provide advice on scientific initiatives and implement the biospecimen access policy; business planning and cost recovery if applicable; space planning and utilization; and equipment and supplies needs assessments [9, Section B.1.1].

3.3. Biobank informatics practices

Informatics for biobanking covers several critical areas: biospecimen tracking; data collection (clinical, specimen quality-related, demographic) and the identification of data elements necessary for each study; data security and protection of privacy; and interoperability of systems [9, Section B.6.1;21]. The interoperability of biobanking informatics systems allows the exchange of data among for example biobanks that are operating within a network. Some other major informatics considerations for biobanks are:

- What types of inventory, tracking, data collection and analysis data will be necessary?
- Will these needs be met using existing institutional systems or will new in-house or commercial systems be necessary?
- Within a biobanking network will data collection and exchange systems be compatible? Will new web interfaces need to be created to collect data?

Best practices for biobanking informatics include recommendations for addressing such issues when planning a new biobanking operation or developing a network of biobanks.

3.4. Economic recommendations

Many biobanking operations were developed with little regard for good business practices or a thorough understanding of the costs to institutions and the investigators who use the biospecimens. Economic recommendations are starting to be incorporated into best practices, including those from the NCI [9, Section B.1.3], because of the recognized high cost of collecting, processing, and storing large collections. Such recommendations include the adoption of standard business practices in order to understand all costs associated with starting and operating a biobank. These costs include personnel, equipment and its maintenance, quality assurance, and informatics/data collection. When such costs are well-understood, a full or partial cost recovery program may contribute to long-term sustainability of the biobank and discourage requests for excessive numbers of specimens [12]. For many studies cost recovery is not appropriate as the biospecimen collection costs are built into the grant or contract that supports the study.

3.5. Quality assurance

One of the major overarching issues in developing biobanking best practices is a quality management plan, comprised of quality assurance and quality control (QA and QC). Definitions of QA and QC for biobanking applications are generally similar to those for laboratories and other organizations that require such plans and monitoring activities [22]. As noted in the NCI Best Practices an effective quality management system requires:

- Equipment maintenance and repair protocols and records
- Training records and staff adherence to training schedules.
- Data management plans
- Formal recordkeeping procedures
- Development of and adherence to standard operating procedures.

The specialized nature of biobanking requires that a standard operating procedures manual describes the following policies and procedures:

- Biospecimen handling
- Laboratory processing
- Shipping and receiving protocols and material transfer agreements
- A record management system
- Building, personnel and biospecimen security
- Safety and waste disposal
- Procedures to investigate, document and report on staff injuries and dangerous exposures
- Equipment maintenance, repair and calibration records.

These policies and procedures should be used to formulate a quality control plan that results in regular audits of the biobank and its management structure to assess adherence to the SOPs. Any deficiencies should be addressed through a formal review of procedures and adjustments made as necessary to correct problems or adapt to new technologies. Documents involved in any quality management system need to undergo an initial approval process and any changes documented and approved under a version control system. Document control systems can either use manual routing and signatures or if resources allow, web-based software that provides automated routing and electronic signatures [23].

The above recommendations assume that resources are available to develop a comprehensive quality management plan. As for other technical best practices some biorepositories lack the resources to implement such plans. For example, a biobank may only consist of one or two freezers in a laboratory or pathology suite. In those situations a quality management plan may be limited to a small number of SOPs, regular freezer monitoring and periodic inventory checks.

4. Ethical, legal and social issues

In recent years public awareness of biospecimens and biobanking has grown significantly. Lawsuits related to secondary use of biospecimens and the nature of informed consent made front-page news [24,25], and a book about the woman behind the HeLa cell line topped the New York Times Bestseller list for months [26]. While such stories have captured the imagination of many, there continues to be a general lack of understanding about biomedical research in general and the contribution of biobanks to the research process. The majority of legal cases and press coverage related to biobanking involve not the technical aspects described above, but the ethical, legal and social issues that are intrinsic to the research use of biospecimens from human research participants.

Biobanking begins and ends with the human research participant who contributes biospecimens to research. Without their donation, the biobank would cease to exist and much research would not progress. Best practices in the ethical, legal and social domain serve three key purposes: to protect the rights and welfare of research participants, to demonstrate respect for research participants and to promote ethically responsible research. While most would agree to the sentiment behind these goals, crafting best practices in support of these principles can be challenging due to variations in legal standards and requirements as well as variation among research participants in terms of their values and opinions related to research and biobanking. Where possible, best practices should also help researchers anticipate potential issues and plan their policies accordingly.

4.1. Governance and custodianship

The issue of "ownership" of human biospecimens has led to several disputes and legal cases [27–29]. The dispute at the heart of most of these cases is who has the right to control the use and distribution of biospecimens, and in some cases, products derived from biospecimens [27–29]. Such cases have been decided based on the facts of the particular case and existing legal constructs within state law, such as gift law. Accordingly, decisions in such cases are generally fact-specific and limited to the jurisdiction in which the case was decided. Instead of focusing on the concept of ownership, some have suggested alternative models, such as custodianship, which focus on the nature of the duty to the research participant [9,20,30]. The NCI Best Practices define custodianship as the "caretaking responsibility for biospecimens that extends from collection through research use." Responsible custodianship requires careful planning and transparent policies to ensure the physical quality of the biospecimens, the privacy of human research participants, and the appropriate use of biospecimens and data.

One key element of custodianship is the development of a governance plan, which describes the oversight and structure of the biobank. The governance plan should describe the roles and responsibilities of key parties involved in the biobank as well as any oversight or management structures in place (Table 1). For public biobanks, the policies and procedures related to access to biospecimens and data are an essential component of the governance plan. In general, biobank access policies should be based on transparency, scientific merit, ethical considerations, and the scientific value of the specimen [9,20,31]. In biobanks where access decisions are complex and numerous, an independent advisory board may be needed to assess the scientific merit of access requests, make final biospecimen access decisions, and resolve potential conflicts of interest. Where practicable, the biobank should make public a description or diagram of its governance model to inform research participants and other stakeholders of the practices in place [9,30].

The governance plan for a biobank should also include legacy or contingency plans to address the handling and disposition of biospecimens and associated data should the resource be terminated for any reason [9,20]. Following any of the events listed in Table 2, an initial assessment should be conducted to determine whether the stored biospecimens still have value for research [9]. If the biospecimen collection is scientifically valuable, but the biobank is unable to become self-sustaining, the biospecimens may be transferred to suitable research facilities using the same decision-making criteria typically utilized in the access process [9,30]. Any transfers of biospecimens must be consistent with human subject regulations and the informed consent under which the biospecimens and data were initially collected and should be carefully documented using material transfer or other similar agreements [9,30].

Table 1
Key issues to consider in development of governance and legacy plans.

Governance plan	Legacy plan
Maintenance of physical integrity of biospecimens	End of the budget period of the grant/ contract or termination of funding
Maintenance of data associated with the biospecimen	Accomplishment of the specific research objectives of the study
Plans and protocols for distribution of biospecimens and/or data to investigators	Loss of a contractor or subcontractor, if applicable
Roles of the biobank manager and the host institution	Loss of management or key personnel, such as if the principal investigator of the biobank leaves the host institution
Mechanisms for oversight and/or review of the biobank	

Table 2
Informed consent elements relevant to biospecimen research.

Element/principle	Regulations or guidance	References
Type of data, whether the biospecimen/data will be identifiable and privacy protections in place	[71]	[9,20,51]
Oversight mechanisms, including access and governance	[71]	[9,30]
How the biospecimen will be used and if secondary research projects are anticipated		[9,30]
Whether biospecimens will be used by commercial/ for-profit entities and whether participant will receive any benefits		[9,30]
Description of what will happen to the biospecimen and data following a request for discontinuation	[72]	[9,20]
Whether results will be returned		[9,63,65,66]
Whether biospecimens and/or data will be shared	[71]	[9,73]

Elements listed in the table are in addition to general requirements for informed consent under 45 CFR 46.116.

4.2. Informed consent

Informed consent has long been recognized as a pillar of ethical research required for adherence to the principles of respect for persons and autonomy [32,33]. In the United States, informed consent is required for any federally funded research study in which investigators obtain data through intervention or interaction with human subjects or if investigators obtain identifiable private information about research participants [34]. Biospecimens collected specifically for a research project through intervention with a research participant would require informed consent, but residual biospecimens originally collected for clinical care may or may not require consent for research use depending on the type of information associated with the biospecimen and whether it would be identifiable. International regulations related to the use of human subjects in research vary widely [35], however international groups recommend informed consent for the research use of biospecimens unless such consent is waived by an institutional review board or ethics committee [20].

Recently, several commentators have questioned the nature of informed consent for research use of biospecimens and whether such consent could ever be truly "informed" given the broad range of potential future uses and the rapidly evolving technology [36,37]. Meanwhile, the US Department of Health and Human Services released an Advanced Notice of Proposed Rule Making (ANPRM) [38] which proposed mandatory informed consent for research using biospecimens and supported use of a one-time broad consent for this purpose. The basic struggle illustrated by this debate is how to provide sufficient information to research participants to allow them to make an informed choice about biospecimen donation, yet maintain the flexibility needed to ensure that biospecimens may be used for future projects as the science evolves.

Empirical studies have begun to shed some light on research participant preferences related to informed consent for biobanking. While the precise numbers vary depending on the population, several studies have demonstrated that the majority of research participants are comfortable with a broad consent that allows for a range of future research [39,40]. These studies reveal that many participants want the opportunity to consent to research using their biospecimens and/or data, but that they are happy to do so only once [39,41]. This general view correlates with some of the recent legal cases in which parents sued state health departments after discovering that blood spots routinely collected for newborn screening purposes were being used in research without parent informed consent [42,43]. In one such case in Texas, a mother who was a plaintiff stated, "To me, this whole thing was about consent. If they had asked me … I probably would have consented. The fact that it was a secret program really made me so suspicious of the true motives, there's no way I would

consent now" [44]. Importantly, other studies have demonstrated that in some cases, research participants are more evenly split between those who prefer one-time consent and those who would prefer specific consent and/or the opportunity to agree to each potential use of his/her biospecimen [41,45].

Given that research participants will likely continue to hold conflicting preferences related to informed consent, how should biobanks develop informed consent policies in practice? One common recommendation is to provide participants with a "tiered consent" which features a number of options and allows participants to select the research uses they prefer [46]. While such a tiered consent does allow participants to experience a greater degree of autonomy, biobanks implementing such a model must ensure that they have the systems in place to honor participant choices. In addition, tiered consents must be carefully structured to allow interpretation and implementation of the choices a participant makes down the road. Another common best practice recommendation is to describe the types of research that are anticipated, but also describe the oversight and governance mechanisms established at the biobank, to include ethical review, access policies, and privacy protections [9,30]. This type of approach promotes greater understanding of biobank operations and the nature of the protections in place while still allowing biospecimens to be potentially utilized for a variety of research projects. Since this broader approach may not satisfy participants who would prefer to consent to individual research projects, the consent should clearly state that biospecimens will be used in a variety of research projects and that participants will not be able to select individual projects. Several sample biobanking informed consent documents are available which address different collection settings [47–49], some of which have been assessed through empirical study of hypothetical research participants [50]. While specific content will depend greatly on the nature of the study, some commonly recommended concepts are highlighted in Table 2.

4.3. Protection of participant privacy

One of the greatest risks posed by biobank participation is informational risks such as loss of privacy or breach of confidentiality. Privacy protection has been highlighted as an issue of concern to biobank participants [45,50,51]. Biobanks should establish clear policies for protecting the confidentiality of participant information. These policies may include data encryption, coding of biospecimens and data, establishing limited access or varying levels of access by biobank employees, use of nondisclosure or other agreements, as well as data security practices [9,20]. Many biobanks employ an "honest broker" model where an individual, organization or system serves as a trusted intermediary to provide deidentified biospecimens and/or data to approved researchers [52–56]. The honest broker serves as a firewall between the biobank and the researchers to help ensure the privacy of participants and the confidentiality of data [52–56]. Biobanks could consider applying for "certificates of confidentiality" to protect identifiable research information from forced disclosure, depending on the nature and sensitivity of the identifiable data associated with the biospecimen [57]. In addition to policies to protect privacy and confidentiality, biobanks must also develop policies to deal with possible unauthorized disclosures that may inadvertently occur.

4.4. Intellectual property

As biospecimens are increasingly recognized as an important scientific resource, some institutions have begun to exert control over biospecimen collections. Variation in intellectual property policies leads to difficulty in sharing biospecimens and data and delayed research. Typically, biobank staff or others involved in the collection, storage or annotation of biospecimens will not be considered inventors and will not have "reach-through" rights to the intellectual property of potential end-users who conduct research with biospecimens [9]. Biobanks should consider use of a material transfer agreement (MTA) or other appropriate agreement as a means of documenting the understanding between the biobank and the end-user about how intellectual property issues will be handled. As the primary agreement between the biobank and the end user, the MTA serves as the best mechanism for documenting acceptable and prohibited uses of the biospecimens and addressing issues related to biohazard precautions; liability and/or warranty; transfer of biospecimens; and applicability of any relevant laws, rules or regulations. Table 3 contains some common terms found in MTAs for biospecimen transfer and several model MTAs are publicly available and may be adapted to meet the specific needs of an individual biobank [58–60].

5. Challenges ahead

Although the development and adoption of biobanking/biospecimen best practices has seen significant progress in the past 10 years much remains to be done to advance the field. Practices are still not well coordinated across international borders and some of the more controversial ethical and regulatory practices are difficult to standardize and turn into practices that will be widely accepted by the biobanking communities.

5.1. International collaboration a necessity

To the extent possible future editions of best practices from various organizations should be better coordinated in terms of content and supported by evidence from published biospecimen research. Best practices have been developed by a number of leading national and international organizations [4,9,20] which generally address most or all of the issues outlined in this review. However the adoption of such practices is rarely well-coordinated, which has resulted in confusion over which practices are preferable or appropriate for particular biobanks or biobanking networks. A number of organizations are attempting to remedy this situation through international coordination of activities. ISBER [61] hosts annual meetings and otherwise through its working groups, best practices and other resources provides a forum for sharing biobanking information. More recently the European, Middle Eastern and African Society for Biobanking and Biopreservation [62] (ESBB) was created to provide similar coordination and educational support on a regional basis.

Table 3
Common material transfer agreement terms for biobanking.

General terms	Provider responsibilities (biobank)	Recipient responsibilities (end-user/researcher)
Descriptions of the biospecimens, derivatives and/or data to be transferred	Disclaimers of liability and warranty for the biobank	Prohibition on using the materials in humans or to identify research participants
Description of intellectual property policy	Assurance that the biospecimens were obtained with appropriate informed consent and IRB approval	Limitations on commercial use (if applicable, may be based on informed consent)
Agreement to abide by appropriate laws, rules, and regulations associated with human subjects and private information	Assurance of the end user's academic freedom and the right to publish research results	Prohibition on further distribution of the biospecimens without prior permission
		Acknowledgment of biobank as source of biospecimens in publications/presentations

5.2. Some issues are difficult to standardize

The development of certain standard ethical and regulatory practices is difficult partly as a result of differing laws and regulations in various countries and states. One of the most contentious issues in both biobanking and biomedical research in general is whether to return research results to participants. There is little consensus as to whether individual-level results should ever be returned and if so, under what conditions and by whom. Advocates for the return of individual research results maintain that research participants should be offered the option of receiving potentially important information about themselves that could impact their health and life choices [46,63–66]. Opponents of sharing individual research results assert that the purpose of research is to generate knowledge rather than provide clinical care and that research laboratories do not necessarily operate in accordance with clinical laboratory standards and therefore could cause harm to participants by returning invalid results or findings of unknown utility [67,68]. While some common principles such as analytical validity, importance to health, clinical applicability, and consent to receipt of the information have been identified by multiple groups as required for return of individual research results [46,63–66], these principles are not universally accepted [67,68] and there is a lack of consensus as to how to interpret and implement each of these broad principles.

Another complex issue is whether consent should be sought at age of majority for biospecimen donors who were minors at the time of donation. Biospecimens from minors may be utilized for research with a parent's permission, however, when the former pediatric donor reaches the age of majority, the parental permission is no longer valid for ongoing research use of the biospecimen [69]. If the research continues to meet the definition of human subject research (e.g. if biospecimens or associated data are considered identifiable) then legally effective informed consent must be obtained from the now-adult donor [69]. However, in many common biobanking models biospecimens are coded such that the donor identity is not "readily ascertainable" per the human subject regulations, but consent would still be possible. It is not clear whether consent at age of majority would be required for research use of "coded" biospecimens. Further, even if consent is not required from a regulatory perspective, it may still be required from an ethical perspective. In one study, adults who were surveyed stated they would not be concerned about the use of their biospecimens after they reached adulthood, however, this study utilized a hypothetical scenario and did not survey actual pediatric biospecimen donors [70]. More research is needed on this important issue to determine participant preferences about consent at age of majority and how policies could be implemented within a biobank setting.

As future editions of best practices from various international organizations continue to be published, they will need to address technical recommendations based on solid biospecimen research data. The more controversial ethical, legal and social issues will require continued negotiations among international biobanking organizations and regulatory bodies in order to facilitate the growing need for biospecimens to be collected and transported across borders and among members of biobanking networks.

Conflict of interests

There is no conflict of interest among authors.

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