Commentary on Improving Biospecimen Utilization by Classic Biobanks: Identifying Past and Minimizing Future Mistakes

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Many classic biobanks collect more human tissues than they distribute, leading to increased inventories, unnecessary storage, increased expenses, and reduced chargeback income. This situation is a result of biobanks operating without well-defined goals, having incorrect views of the potential number of investigators who will utilize specimens, and collection of biospecimens without adequately considering the need for specific tissues by investigators. These deficiencies frequently lead to unrealistic plans for biospecimen utilization and biobanks that are larger than necessary. For example, tissue collections usually are not periodically compared with biospecimen distribution and modified accordingly. An ethical issue has arisen as to the acceptability of consenting patients for the use of their tissues in research without a realistic planned approach to distribution of the biospecimens and their ultimate utilization in supporting biomedical research. These issues and how to minimize them are discussed in this commentary focused on how classic biobanks can improve utilization of their biospecimens.

Keywords: classic biobank, biodistributor, biospecimens, utilization, research

WE CONSIDER CLASSIC biobanks to be entities that collect biospecimens based on the expectation that the biospecimens will be requested in the future by investigators to aid in their research projects. Usually, these biospecimens are obtained from remnant clinical specimens that are not needed for clinical activities, such as diagnosis, and ultimately would be discarded. In contrast, epidemiology (population) biobanks typically collect specimens to meet planned experimental goals, such as the evaluation of screening methods for specific cancers, and prospective biobanks are focused on meeting the requests from investigators for specific biospecimens.

Classic biobanks may either be closed or open with respect to the investigators who can obtain biospecimens. A typical closed biobank may provide biospecimens only to specific investigators who are members of the entity that financially supports the biobank (e.g., a university). Open biobanks may provide biospecimens to any investigator who requests them provided the request is considered “worthy” with respect to the utilization of biospecimens in supporting an investigator’s research.

The classic model of biobanking has remained largely unchanged, even though major problems with biospecimen distribution previously have been identified.^{1–4} Recently, a survey of biobanks in the United States indicated that the

failure to distribute adequate numbers of biospecimens was listed as a great concern of this biobanking community.^{1,2,5} To the best of our knowledge, there has not been a comparable academic peer-reviewed study published focusing on biospecimen utilization outside the United States. A more global study is available online that indicates the underutilization of biospecimens is a problem outside the United States; however, this study is only available online, has not been peer reviewed, and may be subject to conflicts of interest. Of note, publications from the biobanking community in Australia and Europe^{3,6} suggest that the underutilization of biospecimens is global.

The issue of biospecimen underutilization has raised an ethical issue as to the acceptability of collecting biospecimens from consented patients without realistic plans for their effective utilization in research as well as problems with the disposition of unused biospecimens when biobanks close.^{5,6} Although some patients previously were not consented by biorepositories for the use of their de-identified biospecimens in research, the changes in the Common Rule, the General Data Protection Regulations of the European Union, and other similar regulations will increase the number of patients who will be consented. When patients are consented to collect their remnant biospecimens for research, there is essentially an implied social contract between donors

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and biobanks that the biobanks will work to distribute these tissues for use in research. If good faith distribution of biospecimens does not occur, this contract is broken. Nevertheless, based on our consulting experiences, new biobanks continue to be developed frequently without clear realistic approaches and goals for biospecimen utilization. The issue is twofold—one is that too many biospecimens are being collected by biobanks and/or the plans for distributing collected biospecimens are inadequate. Both contribute to biospecimen underutilization.

The survey of U.S. biobanks² indicates that building a biobank with the concept that tissues will be collected and then investigators will use these tissues has not worked! This is supported by the millions of unused biospecimens stored at the National Institutes of Health (NIH) that have been collected over multiple decades, but that today are without realistic plans for their utilization.⁷ These specimens are available, usually with costs, to the research community, but still are not being utilized. In most biobanks, there is an imbalance between collected and distributed biospecimens so the number of unused banked biospecimens will continue to grow. Consider that if a biobank has an inventory of 20,000 biospecimens but distributes only 2000 biospecimens per year, at the current rate of distribution (assuming collections were immediately suspended), the inventory of the biobank would represent a 10-year supply. Herein lies the major flaw in classic biobanking—many biospecimens will not be distributed and hence used in research. Actually, the name “biobank” encourages the hoarding of biospecimens.⁴ We propose the use of the term “biodistributor” to emphasize the more appropriate goal of utilization of biospecimens in research.

Certainly, there are examples that can be cited as to important results that have come from banked collections such as the study of flu pandemics (e.g., 1918) and retrospective studies of “newly identified diseases” such as pneumonia secondary to legionella.^{8,9} Millions of biospecimens usually are not required to study such questions, and if needed, biospecimens that could be used are currently in biobanks of the NIH and other governmental biorepositories. In addition, many types of research, which might be proposed, may be limited in that there is minimal knowledge as to the molecular effects of long-term storage.^{10–12}

Implicit in this commentary is that the underutilization of biospecimens in classic biobanks is a global problem. The following are our views of some of the major mistakes in the operations of classic biobanks and our suggestions as to approaches to avoid these problems, to increase biospecimen utilization, and hence, to increase the impact of each classic biobank on medicine and science.

- (1) There have been failures to establish classic biobanks based on well-defined goals, on determining the pool of potential investigators and on clearly understanding investigator needs.
- (2) Biobanks should not be developed if collections of tissue will not be focused on demonstrable needs to support specific research and/or if the specific tissues are readily available from other sources. For example, there are normal and malignant biospecimens available from multiple sources, such as NIH and National Health and Nutrition Examination Survey (NHANES)^{6,13}; however, such biospecimens may or may not be suitable for use in

all types of research. For example, the available samples may be only biofluids, but solid tissues from cancers are needed by a research project.

The goals of a biobank should be based on identification of current and future biospecimens that are needed by investigators who likely would use the biobank and the specific types of tissues, the quantities of each tissue type, and the tissue preparations that are needed by these investigators. For closed biobanks or for some open biobanks, plans for biospecimen collection may be based on goals of the funding entity; however, these goals may not consider biospecimen utilization and/or may not be appropriate for potential users of available research funding. For example, collecting all available cancer biospecimens may not be appropriate for a closed classic biobank whose potential users study only cancers of the breast and prostate.

Before a biobank is designed, its goals developed, and financial sustainability is planned, it would be important to survey all potential investigators as to their current and future needs for specific types of biospecimens (numbers of subcategories of biospecimens per year). This would identify an intermediate plan for the establishment of tissue collections and the goal for maintenance of a stable potential inventory. The biobank should also plan to rely on other available bio-resources to meet unplanned needs. In this regard, biobanks could rely on open bioresources such as the Cooperative Human Tissue Network, TuBaFrost, and the Telethon Network of Genetic Biobanks. Alternatively, biobanks could establish and participate in collaborative groups so that biobanks do not need to collect all available tissues (e.g., pancreatic cancers might be collected, processed, stored, and distributed from biobank A, whereas lung cancer would be distributed from biobank B).

- (3) Realistic plans frequently are not developed nor followed for distributing biospecimens as a critical component of the design of a classic biorepository or as a new emphasis of operations of an existing biorepository. The distribution or utilization of biospecimens for research should be the primary goal of any biobank; without distribution, a “biobank” is a “biohoard.”⁴ As discussed previously, an active biobank should have a relatively stable inventory.
- (4) At the end of each year, both collection and distribution of biospecimens should be evaluated, matched, and adjusted accordingly. If specific tissues are not requested nor is their need anticipated in the future, similar biospecimens should either not be collected or collected at a greatly reduced rate. In its policies of distribution, a biobank should avoid the view that no research is “worthy” of the samples in its collection; thus, the biobank should consider why biospecimens should be provided before considering why biospecimens should not be provided.
- (5) There frequently are no budgetary consequences of over collecting tissues by a biobank and/or failure to distribute specimens to investigators. Budgets for biobanks will and should be reduced for failure to distribute adequate numbers of biospecimens or to permit inventories to grow beyond foreseeable uses. Specifically, if cost recovery is based on biospecimen distribution, failure to distribute biospecimens should cause budget deficits. Such budgetary problems will be complicated

by overstaffing and/or failure to use staff to focus on the distribution of biospecimens and/or on marketing. Personnel should be assigned to distribution of biospecimens. Overstaffing and hence overcollection will result in uncontrolled growth of tissue collections and increased costs, and hence should be avoided.

The collection of excess frozen biospecimens can be identified by requests for additional freezers or other storage modalities. If the inventory of the biorepository is stable, obtaining new freezers primarily should be limited to replacement of older freezers or a new carefully justified research focus of the biorepository.

- (6) Selection of an optimal stable inventory. The goals of a classic biobank should consider selecting an optimal inventory. The choice of an optimal inventory should be based on multiple considerations based on financial considerations. If the biobank is to contain mature biospecimens for studies of outcomes, it is unlikely that these mature biospecimens will cover all diseases or even all cancers. For cancers, the age of the mature biospecimens will vary with diagnosis. For example, for pancreatic and ovarian cancers, most patients currently do not survive beyond 5 years, so perhaps a mature biospecimen could be considered as 5 or more years.
- (7) For prostate and breast cancers, mature biospecimens would be older, such as 10 or more years. For closed classic biobanks, categories for mature biospecimens would likely follow the research of potential biorepository users. The number of mature biospecimens in a single category also would depend on the type of outcome, risk, prognosis, and diagnosis. Finally, outdating of biospecimens due to known and unknown factors would have to be considered. The factors to be considered in selecting an optimal stable inventory are complex and have to be based on experience in tissue utilization and on financial and resource (space) considerations.
- (8) There has been a failure to base large-scale collections on statistical models that would be useful in minimizing the number of unused specimens in large collections. For example, instead of collecting biospecimens from a million normal volunteers, a statistical subset should be identified that would be adequate to answer most scientific and biomedical questions with a much smaller inventory. Collections based on statistical models should minimize unnecessary costs, resulting in a more cost-effective approach to maintaining appropriate inventories. Attention should be focused on the history of large collections. Large collections of biospecimens that have adequate quality control (QC) performed shortly after collection to define their inventory usually do not run out of biospecimens. Similarly, the design of large collections in the United States frequently has ignored similar available biospecimens in the United States or in other countries (e.g., the United Kingdom Biobank).
- (9) There has been a failure of developers and operators of classic biobanks to recognize that molecular features of tissues thought to be “stabilized” by freezing or fixation/paraffin embedding may not be stable on long-term storage (e.g., more than 10 years). While it is likely that specific molecules in tissues may degrade over time, the details of such degradation is unknown but is likely to vary with the molecule, the tissue, the disease process,

and donor characteristics and tissue processing and storage.^{10–12} Nevertheless, limited evidence suggests that specific molecular features of tissues are not stable during various periods of storage.^{10,11,13–16} Based on the limited studies available, biobanks and investigators should assume that there will be some specific molecular changes in tissues during storage. At a minimum, specimens should be tested by investigators as to the effects of the length of sample storage on the analytes being studied (e.g., plot time of storage of control biospecimens vs. the molecular features being analyzed) to avoid bias.¹⁶

There are several other points that those developing or operating classic biobanks, as well as entities funding biobanks, should consider to improve the efficiency, cost-effectiveness of operations, and their impact on/of biobanks including increasing the utilization of biospecimens. These include the following:

- (a) Obtaining consent from patients to use their remnant biospecimens in future undefined research has varied among biorepositories; however, institutional review board/ethical requirements for obtaining consent for undefined future research of nonanonymized biospecimens have increased in the past decade. In the United States, with changes to the Common Rule, collection of nonanonymized biospecimens by biorepositories for future undefined research will require some type of consent from donors (e.g., broad consent). This will require more attention of biorepositories to ethical issues related to underutilization of biospecimens from consented patients.^{5,17}
- (b) Prospective collection should be considered as an integral component of any classic biobank.^{17,18} This will be necessary as more investigators request fresh viable tissues for their research.
- (c) Biospecimen distribution policies should be developed and compared with biospecimen distribution collections at least yearly. If collections significantly exceed distribution, personnel should be shifted to marketing and distribution.
- (d) The storage of biospecimens should be organized so that collections can be efficiently pruned (i.e., unneeded biospecimens can be discarded cost-effectively).
- (e) The classic biobank should perform QC when biospecimens are collected and processed. This approach updates the inventory of the biobank and facilitates rapid matching of available biospecimens with investigator requests.
- (f) The inventory of the biobank should always be current (e.g., distributed biospecimens rapidly removed) and should include clinical molecular biomarkers (e.g., estrogen receptor [ER], progesterone receptor [PR], human epidermal growth factor receptor type 2 [HER2] for breast cancers) of cancers to aid in meeting rapidly investigator requests.
- (g) Most models of biorepository operations have difficulties with financial sustainability unless there is separate internal or external funding. A focus on increased tissue utilization by reduced collection and increased distribution will aid in establishing financially sustainable “biobank” operations.
- (h) In establishing advisory committees for organizations that are funding biobanks, do not include advisors who may have conflicts of interest (e.g., those who would

benefit from increased collections or storage of biospecimens).

- (i) To incorporate new ideas as to the design and efficient operations of biorepositories, including increased biospecimen utilization, biobanks should participate in biorepository organizations such as the International Society for Biological and Environmental Repositories (ISBER) and/or other expertise networks.
- (j) In order that biospecimens will be more effectively utilized in supporting biomedical research, biobanks should be evaluated on the distribution of biospecimens, rather than on collection and banking of biospecimens. This will increase the biomedical impact of biorepositories.
- (k) The impact of the biorepository on science and medicine should be closely followed to demonstrate the usefulness of the biorepository. At a minimum, publications and patents resulting from operations of each biorepository should be identified.
- (l) There must be a better understanding of biorepository sciences so that limitations on the use of biospecimens provided by biobanks can be identified and correct decisions can be made as to how to store, analyze, and utilize biospecimens. In the near future, whether or not the design of the classic biobanking model has to be reconsidered may depend on the stability of biospecimens during extended storage.
- (m) Biorepositories and investigators have to understand that bias may be introduced to studies relying on older biospecimens if variable changes in the molecules being studied occur during various lengths of storage.

Our comments are focused on the model of the “classic biobank” and not on epidemiological biobanks or on biobanks focused on rare tissues; however, our concerns of the stability of specific molecules on long-term storage and specimen utilization after original epidemiological/population questions are completed are applicable to these models and should be addressed. We are not advocating abolishing classic biobanks whose functions are critical to the development of biomedical research; instead, we recommend being smarter in new designs planning and operations of classic biobanks, as well as in novel approaches to biobanking.^{18,19}

In summary, it is very important that the appropriate collection and distribution of biospecimens and/or their associated data be a major goal of all classic biobanks. If the collection of biospecimens significantly exceeds biospecimen distribution, the imbalance will rapidly lead to an expanding inventory. This will cause excess specimen storage and associated increased expenses, will reduce income associated with cost recovery, will threaten financial sustainability, and will inhibit biomedical research. Of importance, long-term storage may have unknown effects on the molecular stability of biospecimens, and hence, their usefulness in research. Failure to adequately distribute specimens may cause ethical problems because expectations of patients who have consented to donate biospecimens to improve medical care are not being met. To reduce any imbalance between biospecimen collections and distribution, personnel should be shifted from collection of biospecimens to marketing and distribution or if necessary, the biobank should be downsized.

Acknowledgments

Supported in part by the Cooperative Human Tissue Network (CHTN 1UM1CA183728 and 5UM1CA183728) and the Tissue Procurement Shared Facility of the UAB Comprehensive Cancer Center (P30CA13148-41), the Pulmonary Hypertension Breakthrough Initiative (1R24HL123767-03), and the Hepato/Renal Fibrocystic Diseases Core Center (P30DK074038).

Author Disclosure Statement

No conflicting financial interests exist.

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