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The Utilization of Biospecimens: Impact of the Choice of Biobanking Model

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The term research ''biobank'' is one of multiple names (e.g., bioresource, biorepository,) used to designate an entity that receives, collects, processes, stores, and/or distributes biospecimens or other biospecimen-related products (e.g., data) to support research. There are multiple organizational models of biobanking used by bioresources, but the primary goal of all bioresources should not be simply to collect biospecimens, but ultimately to distribute almost all collected biospecimens and/or data to support scientific research; bioresources should serve as ''biodistributors'' rather than ''biovaults.'' The appropriate choice of model is the first step in ensuring optimal biospecimen utilization by a bioresource. This article discusses some of the different models that may be used alone or in combination by a bioresource providing biospecimens for research; it describes the factors affecting the choice of the most appropriate model or models, the advantages and disadvantages of the various models, and a discussion of the impact of the choice of the model on biospecimen utilization. Frequently, problems with biospecimen utilization are not caused by any single model, but rather a mismatch between the choice of model and goals of the bioresource, and/or problems with the subsequent design, goals, operations, and management of the bioresource after a model is selected.

Keywords: prospective, biospecimen, utilization, biodistributor, biobank, biorepository, bioresource

Introduction

''Biobank'' is one of many terms (e.g., biorepository, biovault, bioresource) used to designate entities that are involved in biobanking. While many definitions exist for a biobank and the activities that are involved in biobanking, we will use the definition of the International Society for Biological and Environmental Repositories (ISBER): ''An entity that receives, processes, stores, and/or distributes specimens, as needed. It encompasses the physical location as well as the full range of activities associated with its operation.''[1–6] We consider that a component of a biobank includes its inventory of biospecimens.

Biobank also is a term that has been used to describe entities involved in providing clinical biospecimens for medical care, such as human organ transplantation as well as the biobanking of plant and animal biospecimens for various uses. This article focuses only on entities that are involved in biobanking of human biospecimens to support biological and biomedical research; however, some of the discussions also are applicable to other types of biobanking[5–7] as are best practices.[5–7]

To some, the term biobank may confer a connotation of acquisition and storage, but not necessarily of distribution and use.[3,4] This is why we prefer the term bioresource.[4] For clarity and to emphasize the goal of distribution and use, this article will use the term ''bioresource'' instead of ''biobank,'' except when referring to a specific model of a biobank, the classic biobank. We use the term, ''biobanking,'' to refer to the overall activities performed by a bioresource.[4]

In this article, we focus on various models of acquiring and distributing biospecimens (biobanking models) and the impact of the choice of biobanking model on biospecimen utilization from a bioresource. Note, a bioresource is not a ''model'' in and of itself, and may not be ''pure'' with respect to the primary model selected. The bioresource may incorporate components of several biobanking models, but usually follows a primary model. The major goal of acquiring human biospecimens for research should be the use of the biospecimens in research, including the distribution to researchers of most of the acquired biospecimens, components of biospecimens, and/or data. However, such a goal may not be a high priority of some bioresources.[3,4,8,9]

Optimal biospecimen utilization is essential for bioresource sustainability; however, both surveys in the United

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States and internationally have identified concerns regarding biospecimen utilization by bioresources.[10–12] Biospecimen utilization is affected by many factors, including the choice of biobanking model.[1–16] One of the first steps in the creation of a bioresource should be to ensure optimal biospecimen utilization by first identifying the scientific goals that the bioresource is intended to meet and to select the most appropriate biobanking model(s) to meet these goals. It is our view that too often researchers build a bioresource based on acquiring the biospecimens that are available for collection at their site(s) with insufficient consideration of the intended use of the biospecimens in research; potential needs of investigators/customers; and development of a stable inventory of biospecimens sometimes are not adequately considered.[8,9] Identification of the scientific needs for specific biospecimens should include determining that the selected biospecimens are not readily available from other sources.

In this article, the main focus is on five models of acquiring and distributing biospecimens and the impact of the choice of each model on biospecimen utilization. Each of these models has distinct characteristics as to their operations and approaches. These five models are the prospective model, the classic biobanking model, the population based model, the data focused model, and the clinical archival tissue model. A brief review of the characteristics and differences of each of these models is shown in Table 1. This article also briefly discusses other types of biobanking models that are amalgams of the goals of the five primary models; however, these models may have different distinct goals and functions. These ancillary models include the clinical trials model, the advocate model, the storage model, the virtual model, the research-consortium model, and the ''unnamed'' model.

It is important to note that a given bioresource may employ different aspects of multiple models for acquiring and distributing biospecimens. For example, a classic biobank may utilize a prospective collection component to meet the increased demand for fresh viable biospecimens obtained prospectively.[8] Similarly, prospective bioresources may incorporate limited, short-term biobanking to increase their efficiency.[8]

Beyond the choice of models, it is our observation that there are several aspects of operations and management that affect biospecimen utilization and are common to many of the bioresources that acquire and distribute biospecimens. These include the overall goals, available resources, approaches to informed consent, and infrastructure. Typically, a general model may be selected based on the bioresource's main goals that may determine the operations of the bioresource. For example, the prospective model is not characterized by just collecting a designated group of defined biospecimens prospectively to meet a defined project, but primarily by being ''investigator centric.'' We consider this model to be investigator centric because biospecimens and associated data are collected prospectively to meet individual researcher's predefined needs/requirements at the time the biospecimens and associated data are collected.

Being investigator centric affects all aspects of the model's use in a bioresource, including finances, governance, goals, infrastructure, operations, informatics, and importantly, a focus on distribution of biospecimens that have been collected based primarily on investigator requests.[8] In contrast, a classic biobanking model is biospecimen centric and includes collecting a range of specific biospecimens and waiting for investigators to request them; also, some biospecimens are collected and banked to acquire associated data (mature) for outcome studies. Other biobanking models are ''project centric'' such as some virtual models and the unnamed bioresource, discussed subsequently, while ''population centric'' and ''data centric ''describe other models. Of importance, the existence of each biobanking model probably has a reasonably established purpose to exist.

The selection of a primary model affects tissue utilization. The primary model affects the design, goals, success, and sustainability of a bioresource, but typically these aspects are issues for the sponsor(s), developers, and operators of the bioresource to determine. We again emphasize a bioresource is seldom pure as to its primary model and may incorporate components of multiple models.

For example, the clinical trials model is used by a bioresource to collect biospecimens from one or more clinical trials. These biospecimens aid in evaluations of the clinical trials. Unused biospecimens may then be stored for future use, which may involve additional evaluations of the clinical trial in the future, but also other undefined research. The biospecimens of a bioresource using the clinical trials model usually are acquired as project centric rather than biospecimen centric, or investigator centric.

In addition to the purpose and goals of the bioresource, the available resources and infrastructure may affect the scope of activities and hence, distribution and use of biospecimens. Usually a bioresource is established with specific start-up funds and a subsequent yearly total budget. These financial resources limit the extent of functions and capabilities, but not necessarily the primary model selected. Funding, however, may greatly impact biospecimen utilization regardless of the model employed by a resource.

Biobanking is a very expensive process and the sharing of costs between the bioresource and the investigator depends upon the financial support of the bioresource by all of its sponsors. If the bioresource must be independently sustainable, the cost that must be charged to investigators might be considered by them to be too high; as a result requests for biospecimens could be greatly reduced. However, the processing fee charges to investigators sometimes represent only a small-to-moderate component of the overall costs of their research. The sponsors of the bioresource must make a decision on sustainability. In part, the cost to investigators may be reduced by mini grants that provide cost support to them for the use of any component of infrastructure.

Regardless of the model chosen, access procedures and policies may affect biospecimen utilization, as explained elsewhere.[16] Sometimes access procedures and policies may be established or operationalized in ways that are too restrictive. Sometimes, for example, Tissue Utilization Committees, sponsors, or others involved in the governance of a bioresource may establish policies that are too stringent, restrict priorities for biospecimen distribution, or limit access to a defined group of investigators. This of course may reduce cost recovery and hence, bioresource sustainability. If even partial self-sustainability is a goal, a cost recovery plan must be established and this plan must include an emphasis on tissue utilization.

Subsequently, we further describe some of the major attributes of each of the various models of biobanking that

Table 1. Characteristics of Five Main Models of Bioresources

	Prospective Model	*Classic Biobanking Model*	*Population Based Model*	*Data Focused Model*	*Clinical Archival Tissue Collections Model*
Biospecimen and Data Collection	Biospecimens and data collected to meet individual investigator needs "Investigator Centric"	Biospecimens and data collected according to pre-defined criteria based on intended use and goals of the overall bank "Biospecimen Centric"	Biospecimens and data are collected from selected donors based on statistical samples from a healthy population/subpopulation or of patients with a specific disease category. Primarily, these studies collect biospecimens that are bodily fluids and occasionally tissue microarrays "Population Centric"	Focuses on generation, storage and distribution of data from the analysis of biospecimens rather than the biospecimens per se "Data Centric"	Biospecimens and associated data are obtained from clinical archives such as those managed by pathology "Biospecimen Centric"
Advantages	Most biospecimens are distributed and used for research Collection procedures can be tailored to meet an individual investigator's needs Flexible model that allows a more rapid response to changing medical care, science, technology and methodology Lower storage requirements Less long-term effects of storage on molecular and other types of analyses Facilitates sustainability	Clinical and other follow up data may be available when biospecimens are provided Large numbers of biospecimens may be readily available May permit the selection of large cohorts to initially evaluate molecular biomarkers as to risk, diagnosis and prognosis in "mature" biospecimens	Approach can provide samples from a healthy population before a disease develops to permit identifying predictive biomarkers for risk and early diagnosis and/or the success of screening methods Alternatively, the population approach can focus on newly diagnosed patients with a specific disease to evaluate predictive biomarkers of risk diagnosis or prognosis and obtain large cohorts with a specific disease. Biospecimens from a prospectively collected cohort can be used for validation studies of predictive biomarkers	Analyses of biospecimens are performed under the control of the bioresource which can be accomplished relatively rapidly under standardized procedures Minimizes biospecimen storage requirements because large amounts of biospecimens need not be retained once data are generated Can maximize knowledge generation from biospecimens that are non-renewal resources by facilitating extensive data sharing with many end users	Large numbers of biospecimens may be readily available with extensive clinical annotation and follow-up data

(*continued*)

Table 1. (Continued)

	Prospective Model	*Classic Biobanking Model*	*Population Based Model*	*Data Focused Model*	*Clinical Archival Tissue Collections Model*
Disadvantages	Clinical or other follow up data may not be immediately available, except for archived paraffin embedded biospecimens because other biospecimens are not stored for any significant length of time. Large numbers of biospecimens may not be readily available because biospecimens are distributed as they are collected. Collection of biospecimens for complex requests and/or rare diseases may be relatively slow	Many more biospecimens may be collected than ever used for research Biospecimens are collected using pre-defined, fixed SOPs based on the current state of the science and/or methodologies that: 1. May not meet the needs of current investigators who require biospecimens to be collected in other ways, 2. May not meet the needs of investigators in the future due to changes in science, medicine, technology and methodology Banked biospecimens may degrade over time; long term storage may have adverse effects on some molecular features or effects of storage may be unknown Large storage-inventory requirements	Tends to be very expensive and unless great care is taken in population selection biased results may be obtained May require a long time to reach its endpoint Unless they are tied to the development of a specific disease, most biospecimens collected may never be used in research	May require extensive IT infrastructure for storage of data May be less useful for basic, developmental and translational studies that require the biospecimens themselves rather than data generated from the biospecimens Knowledge generation may be confined to certain areas because frequently only data are distributed and the data that are distributed may be limited to those generated by the biobank using certain pre-defined methodologies May be limited by the types of biospecimens collected (e.g. bodily fluids)	Biospecimens are limited to those collected during routine clinical care and may be affected by the treatment process Biospecimens may not be suitable for some types of analyses because of the preservation methodologies utilized Biospecimen utilization may be limited because many clinical archives contain only paraffin embedded material
Types of Studies Best Suited For	Basic and developmental studies; translational studies using archived paraffin-embedded material for which clinical data may be available	Studies requiring significant clinical or follow up data, large number of biospecimens, and/or biospecimens from patients with uncommon or rare diseases or conditions If distribution is emphasized, can also support basic, developmental, and translational studies	Biomarker studies of risk, diagnosis (early detection), and prognosis. Success of screening approaches; studies of changes in a population due to environmental exposures; health of the population; nutritional effects on the population	Studies utilizing genetic, genomic data, or other types of data generated from biospecimens which frequently are bodily fluids.	Basic and developmental studies;studies of diagnosis, prognosis and response to treatment because extensive clinical annotation and follow-up data may be immediately available. Studies of uncommon and rare diseases because greater numbers may be available from long term archives

may be employed by bioresources and the impact of the choice of model and design on biospecimen utilization.

Prospective Model

The prospective model always has biospecimen distribution as its highest priority because in this model, biospecimen collections are directly tied to investigator requests; thus, this model is ''investigator centric.''[8,9] Specifically, biospecimens are not collected until there is a request from an investigator for a specific type of biospecimen.[17] The investigator specifies their biospecimen needs and requirements and a standard operating procedure (SOP)/protocol is developed for that specific investigator. For example, investigators indicate the specific diagnosis, the number of biospecimens, biospecimen size, and biospecimen processing requirements (e.g., freezing). Other components of the requests may include annotation, storage, and how the biospecimens are to be shipped.

The investigator-centric characteristics of this model affect all aspects of the use of this model when employed by a bioresource, including the goals, management, operations, and infrastructure of the bioresource. For example, the approach to informatics focuses primarily on investigators and their request requirements for biospecimens; this is a different informatics focus than that of other biobanking models.

When a request (order) is made, the investigator agrees to pay a fee to cover a portion of the cost of procuring and distributing the biospecimens collected according to the investigator's specific requirements. After relevant agreements are completed, biospecimens are collected and distributed to the investigator. Because the number of biospecimens collected is usually equal to the number requested by an investigator, in most cases, almost all collected biospecimens are distributed for research.

For efficiency, during the collection of investigator-requested biospecimens, bioresources using the prospective model sometimes collect more biospecimens than necessary to meet an investigator's request. These extra biospecimens may be banked to meet future investigator requests. In addition, after collection and quality control (QC), some biospecimens may not meet an investigator's request in that the biospecimen diagnosis may be different from the surgical preliminary diagnosis. Similarly, the remnant biospecimens available after clinical requirements may be inadequate for some requests, but not others.

These ''excess'' biospecimens as well as the paraffin blocks used in the QC of each aliquot may be retained by the bioresource in its inventory. Thus, in the prospective model, most biospecimens are collected by the bioresource because of current investigator requests for specific biospecimens and distribution of these biospecimens is the primary goal. In reality, the typical prospective bioresource frequently does not use a pure prospective model, but will adapt the model to meet its needs. Specifically, for bioresources using primarily the prospective model, features of other models may also be used as part of the design, goals, management, and operations of the bioresource. Prospective bioresources may also obtain requested biospecimens for distribution from bioresources using other models of biobanking being employed at their location. For example, a bioresource employing primarily a prospective model may also obtain biospecimens from a classic biobank at the same institution or even from classic biobanks outside the institution with which the prospective bioresource has developed a working partnership.

As an example of a prospective request, an investigator may ask for 25 cases of colon carcinoma, frozen in optimum cutting temperature compound in 0.2–0.3 g aliquots. Other requirements of this investigator may include temporary storage in liquid nitrogen vapor and shipment on dry ice. An annotation, including grade, stage, smoking history, history of inflammatory bowel disease, and family history of cancer, is requested. Ultimately, these requirements would define the specific biospecimens collected and distributed to this investigator and would be a component of the SOP. More details of the prospective bioresource are provided in a separate article of this special issue.[8]

The prospective model has both advantages and disadvantages. As previously mentioned, most biospecimens that are collected are distributed and used for research because they are collected specifically in response to a researcher's request. Additionally, storage requirements are minimized because biospecimens are not accrued and banked for any significant amount of time; for most biospecimens, this also reduces molecular changes that may occur secondary to storage.[1,8,14,15] Because biospecimens are collected according to a researcher's specific request in real time, the model is more flexible in meeting rapid changes in biospecimen collection and handling secondary to new developments in science, medical knowledge, technologies, and methodologies such as individual cell sequencing. Importantly, the prospective model avoids ethical issues of specimens from consented patients not being utilized in biomedical research to improve patient care.[12]

There are also several disadvantages of the prospective model. Specifically, follow-up data are not readily available because biospecimens are distributed soon after collection rather than being held until such data can be obtained (i.e., allowing biospecimens to ''mature''). Nevertheless, outcome data can be made available for some distributed biospecimens if enough time has passed after distribution. Thus, the prospective model is not generally useful for studies that evaluate clinical outcomes involved in the assessment of risk, diagnosis, or prognosis.[18,19] Another disadvantage is that a large number of biospecimens typically are not immediately available for investigators because, in a prospective model, most biospecimens are not collected until after they are requested.[8] In a bioresource using a prospective model, some biospecimens may be available from other sources that may also be using a prospective model. Similarly, depending upon the prospective bioresource operations and investigator requests, some biospecimens may be available from temporary storage.

The collection of specific biospecimens may also be very slow if the biospecimens are from less common diseases and requests for rare biospecimens may be impracticable to meet. Complex requirements of investigators may also greatly reduce availability and increase the time of accrual.[8] For some of these reasons, a prospective model is most useful for basic, developmental and exploratory research that does not require immediate availability of clinical follow-up of patient outcomes (mature biospecimens) and/or an immediate availability of a large number of biospecimens.[8] Some more specific details concerning the operation of a prospective bioresource are discussed elsewhere.[8]

A prospective bioresource can alleviate some of the abovementioned disadvantages by operating as a group of cooperating sites, such as the Cooperative Human Tissue Network (CHTN), in which difficult-to-meet requests can be shared among bioresources operating with similar models and procedures.

The success of prospective biobanking is represented by the CHTN, which, since 1987, has operated as a prospective distribution network.[8] By 2012, the CHTN had distributed over one million biospecimens to support the research of a wide range of investigators.[8]

Classic Biobanking Model

The classic biobanking model is biospecimen centric and is a model that has acquisition of biospecimens as its main focus. Classic biobanks fulfill critically important needs in biomedical research[8,9,20,21] and have many advantages.[8,9] They collect and store biospecimens and data for future research use and have available or may collect rapidly extensive outcome data associated with their mature biospecimens. This permits investigators studying clinical outcomes and their prediction by biomarkers of risk, diagnosis, or prognosis to obtain large retrospective cohorts to determine if a putative predictive biomarker is potentially useful and warrants additional study.[18,19]

The classic biobank may also be able to provide investigators with biospecimens from relatively uncommon and/or rare diseases to support research in these conditions. On initial request, they may also be able to provide relatively large number of biospecimens.

Classic biobanks may be focused on collecting many types of biospecimens or limit their collections to a few diagnostic categories (e.g., paraffin blocks of prostate cancer); this choice is based on experience, goals, resources, investigator requests, and availability of specific biospecimens.

The model of the classic biobank is very sound, but some classic biobanks have been inadequately designed and managed, and their operations have not facilitated tissue utilization.[8,9] There are several issues. One is that a goal for a stable inventory of biospecimens has usually not been established so that inventories continue to increase.[8,9] A key point is that more biospecimens do not necessarily make a better biobank. This also is complicated by a lack of understanding of unknown and uncharacterized degradative changes during long-term storage of biospecimens.[14,15] In addition, as science, methods, and medicine advance, older biospecimens may no longer be needed or requested. To maximize biospecimen utilization, a classic biobank should set its collection priorities based on estimates of the number of biospecimens that are necessary to address the primary research questions concerning the diseases and/or conditions of interest that the biobank is designed to support as well as those biospecimens needed by the intended users.[3,4,9,10]

It is our view that there is often an inadequate focus on biospecimen utilization by some classic biobanks, including distribution of biospecimens to a wide range of investigators. Some biobanks may be closed to extramural investigators so biospecimens are not provided to investigators outside the primary site of operations, resulting in inadequate sharing. This is an issue that usually is controlled by the sponsors.

A classic biobank typically collects biospecimens using one or more predefined SOPs that may vary with the type and available sizes of biospecimens that are likely to be collected (e.g., because of lesion size 0.1 g of breast cancer versus 0.5 g of ovarian cancer). Biospecimen acquisition, including the SOPs of this model, may be based upon the biobank's experience as to prior requested biospecimens and preparations. When an investigator requests biospecimens, they may only have access to the biospecimens that are in the current inventory of the classic biobank; however, the SOPs under which the biospecimens have been collected may or may not meet the exact requirements of a requesting investigator. For example, a biospecimen in the inventory may be too small or the biospecimen may have been collected using SOPs, such as being stored in RNA later that do not meet the investigator's requests. This inability to match investigator-specific requests with the inventories of classic biobanks may reduce biospecimen utilization.

Because large numbers and types of biospecimens are often collected and stored in classic biobanks, it may also be problematic to identify investigators who may need these specific banked biospecimens.[16] The availability of a computerized inventory of the biospecimens of the biobank (i.e., a catalog) can aid investigators in selecting the most appropriate biospecimens to meet their needs; this coupled with effective marketing may be very important for classic biobanks to ensure effective biospecimen utilization.[8,9,16] Of note, an available inventory may not aid those investigators who do not understand issues related to the use of various preparations of biospecimens in research.[8,9,14,15,20–22]

When biospecimen collection outpaces biospecimen distribution, the inventory of the biobank will grow.[9] For example, if the distribution is only 50% of each year's collection and the collection rate is constant, after 4 years, the inventory will have increased by two times the collection rate. A sign of a constantly increasing inventory is an expanding need for additional freezers or other storage modalities. In the design and management of a classic biobank, careful consideration should be given to future storage capacity and deciding when to decrease efforts in biospecimen collection with a shift of personnel and resources to more aggressive marketing activities and distribution.[8,9,16] Some prediction of a required and optimal inventory is necessary.[22] The best classic biobank is well designed and active with a strong focus on distribution and achieving an equilibrium between collection and distribution. Thus, it has a stable inventory that is also designed to maintain mature biospecimens.

Such a classic biobank is critical to the support of biomedical research, especially translational research on biomarkers and other research requiring clinical and/or outcome data, which are typically unavailable from prospective bioresources.[8,9,20–22]

Population Based Model

A population based model is a different model than the prospective or classic biobanking models. This model typically is designed to answer specific questions related to features of populations or subpopulations and so can be considered population centric. A bioresource based on the population model also uses aspects of a project-centric model in that it usually is focused on one specific project. Biospecimens are obtained from a selected number of volunteers; single biospecimens or longitudinally collected

biospecimens may be obtained. The biospecimens are usually aliquots of bodily fluids, such as blood, urine, and saliva, and/or buccal swabs. Most importantly, extensive information on the demographics and health of the population is typically collected.

The population based model is often used for epidemiological or environmental bioresources. Some epidemiological studies using this model may focus on specific health changes in a population over time such as the development of Type 1 and Type 2 diabetes mellitus. Alternatively, this model may be used for environmental studies to identify the presence of xenobiotic agents, especially potential hazardous xenobiotics accumulating in human biospecimens. A separate use of the population based model is to develop prospective cohorts of patients with specific diseases, defined outcomes, and optimally collected biospecimens. Such cohorts are critical for the prospective evaluation and validation of predictive biomarkers of risk, diagnosis, and prognosis of a disease such as cancer.[18,19]

One example of an epidemiological bioresource that has collected longitudinal biospecimens is the Prostate, Lung, Colorectal, and Ovarian (PLCO) bioresource.[23] About 3 million longitudinal samples of blood were collected from about 155,000 age-controlled healthy volunteers with the goal of evaluating the screening methods for these cancers and for studying the development of cancers of the prostate, lung, colon, and ovary.

Subsequently, some patients provided samples of buccal swabs. In addition, aliquots of paraffin blocks from some cancers developing in patients in the PLCO trial were obtained and used to construct tissue microarrays. As with many epidemiology bioresources, there is an extensive annotation of patient characteristics. When a cancer developed in a patient of this population, the biospecimens collected before tumor development were made available to requesting investigators to identify potential biomarkers of cancer development, early diagnosis (detection), screening, and/or to study other tumor-related parameters.

The goals of epidemiology studies and their associated bioresources may require biospecimens to be maintained over relatively long periods before they can be analyzed completely to reach an endpoint. Because only a certain proportion of the study population may develop the diseases studied, there may be low utilization of these nondisease-associated biospecimens. For example, in the PLCO bioresource, samples from individuals who did not develop cancers were not in great demand and have not been utilized as extensively. Specifically, in the PLCO, the depletion rate by 2015 was 5% of all biospecimens and 13% of biospecimens from cases developing cancers.[23] However, changes were made to reduce the depletion rate of samples used for DNA extraction (buccal swabs and buffy coats) by requiring some DNA extracted by investigators from these samples to be returned to the bioresource.

Another example of a population bioresource is the ongoing National Health and Nutrition Examination Survey (NHANES).[24] This study involves participant interviews and examinations and collection of blood and urine samples from up to 5000 adults and children each year. Studies using biospecimens from NHANES were able to demonstrate that discontinued use of lead as a gasoline additive reduced blood levels of the xenobiotic, lead, in the population of the United States of America and separately that sodium consumption in the United States of America has been too high.[25,26] Thus, NHANES is a population study with both health and nutritional endpoints as well as environmental endpoints. As in the PLCO studies, most biospecimens collected by NHANES have not been utilized beyond initial goals and there is a great desire by NHANES to utilize these biospecimens in other projects, including the ''All of Us'' Program[27] discussed subsequently.

One of the reasons epidemiology bioresources may have unused specimens is that many of the specimens that are collected, typically may not be associated with a disease process and hence, are not in great demand because their research uses are limited. It is important that there is extensive marketing of remnant biospecimens at the conclusion of epidemiological studies to promote optimal biospecimen utilization. Because of their extensive associated epidemiological data, studies like the PLCO and NHANEs especially may be useful as controls for investigators as well as being repurposed to study non-neoplastic diseases.

In addition, specimen utilization would probably increase if the application processes for nondisease-associated biospecimens or other biospecimens, for which there are histories of few requests, were simplified, and did not require committee decisions.

The All of Us research program is a population based program that currently is emphasizing acquisition of bodily fluids, especially from minority and rural populations. The approach to collection does not seem to be based on epidemiology, but the numbers should be large enough so that biospecimen selection could follow epidemiological standards. It is not clear at this juncture how well the biospecimens will be utilized because many of the biospecimens may not be associated with a disease, particularly since large numbers of biospecimens from younger populations may be collected.

The population based model is also incorporated in bioresources that focus on identification of potentially hazardous xenobiotic agents in various populations. As expected for a population model, demographic, and in some cases, interview information may be obtained. Changes of specific xenobiotics in human biospecimens over time is very important to the health of any population. In general, monitoring of human biospecimens for toxic substances in the United States of America relied on national monitoring from 1970 to 1990, including the National Human Monitoring Program. Similar programs in other countries include the biobank of the German Human Biomonitoring Commission.[28,29] NHANES also plays a role in the environmental monitoring of xenobiotics.[25]

The biobanking of human biospecimens by the National Human Monitoring Program had multiple technical problems.[28] The last report on its environmental monitoring was issued in 2009,[30] but exposure tables continue to be issued with the last update in 2018.[31] Currently, grants also are made to selected states for environmental monitoring such as the Biomonitoring Exposure Study in California. In addition, environmental screening is facilitated by monitoring of soil, plants, and animals (e.g., current Mussel Watch Program of the National Oceanic and Atmosphere Administration).[32]

There are few adequate descriptions of biospecimens in current environmental bioresources or their availability to

investigators. As with some of the other models that may be designed to meet the requirements of a specific research project, every effort should be made to market the availability of unused biospecimens from any population bioresource, including environmental bioresources. Access should be as simple as practicable.

Data Focused Model

The data focused model usually does not emphasize the distribution of its biospecimens to investigators, but instead, the distribution of research data obtained from acquired and analyzed biospecimens. Thus, this is a data centric model. Bioresources using this model also typically use some aspects of a population based model to acquire the biospecimens from which molecular components are extracted and analyzed. These extracts are analyzed, usually under the control of bioresources. Organized datasets generated from biospecimens are available to researchers based on the various analyses that may be performed. The best example of a bioresource using this model is the United Kingdom Biobank Limited, which is a nonprofit company/charity funded primarily by two organizations—The Wellcome Trust Limited and the Medical Research Council.[33,34]

Its principal objective is ''improving the prevention, diagnosis, and treatment of a wide range of serious and life-threatening illnesses—including cancer, heart diseases, stroke, diabetes, arthritis, osteoporosis, eye disorders, depression, and forms of dementia.''[34] By July 2010, 500,000 adult healthy volunteers had been recruited from Great Britain, but most were of European descent. Blood and urine samples and clinical information were obtained from these adult volunteers; the plan is to follow their health for up to 30 years.[33,34]

Blood and urine are being analyzed (e.g., 821,000 single nucleotide polymorphisms [SNPs] analyzed on each blood sample as of July 2017) and the results will be made available to registered investigators (7500 were registered with accepted projects as of April 2017).[33,34] This is an interesting and sound model in that samples are analyzed by laboratories funded by infrastructure of the model and consistent data are generated for potential evaluation by outside investigators.[35] Costs to investigators are based on cost recovery; in general, data costs are about £ 1500 plus value-added tax. Marketing appears to be online and by published articles. This is likely to be a very important model that may be employed in multiple other countries. Active marketing may improve the utilization of data focused bioresources.

One of the advantages of some bioresources using the data focused model is that assays of biospecimens may be performed relatively rapidly and hence, this might minimize molecular changes on storage or keep molecular changes relatively consistent as biospecimens are extracted and analyzed together. Also, the storage requirements for the biospecimens in the long run could be less than the classic biobank model because large amounts of material that have been extensively analyzed, may not be retained. Storage of the immense amount of data being generated and shared does and will utilize a very extensive informatics infrastructure.

Clinical Archival Tissue Model

The clinical archival tissue model can be considered a unique model of biobanking that is biospecimen centric. The biospecimens in the clinical archive have been removed during therapeutic procedures and have been diagnosed as to the presence or absence of diseases. Although these biospecimens were initially used in diagnosis, they are still important to and useful in future patient care. They also are critically important to biomedical research and to advance medical care, including the development of precision medicine.[36,37] It is estimated that there are hundreds of millions of such biospecimens in pathology archives.

In the United States of America, clinical archival biospecimens are usually fixed in 10% neutral buffered formalin (NBF) and paraffin embedded (formalin fixed paraffin embedded [FFPE]); however, European countries are working on an alternate fixative. Of note, some countries, such as France, encourage the use of cryopreserved biospecimens in diagnosis and research (reviewer comment).

Archival clinical biospecimens typically are under the control of the Department of Pathology and their ownership in the United States of America has been determined to be the institution that collects, processes, and stores these biospecimens.[38] In the United States of America, for accreditation of pathology laboratories, the College of American Pathologists requires that clinical FFPE blocks be maintained for at least 10 years; however, many academic pathology laboratories store their biospecimens for longer periods. As precision medicine advances, the required time of 10 years may be increased.

Maintenance of the archival biospecimens is necessary to address legal issues if there is a dispute regarding medical care. These biospecimens also must be maintained to answer future questions concerning medical care. For example, these biospecimens can be used to determine if cancer expresses a potential therapeutic target for use in precision medicine, or if new information may support a new categorization of a disease than that originally described. Research using these archives is critical in developing new clinical protocols for precision medicine.

One of the unique values of clinical archives to biomedical research is the historical information and outcomes associated with the biospecimens. Specifically, an extensive clinical history and outcome can be obtained on most of these biospecimens.

In a clinical archive, there are many biospecimens that are available on most diagnostic categories. Together with biospecimens from other clinical archives, this permits the association of biomarkers with outcomes. Thus, biospecimens from these archives are important in identifying biomarkers of diagnosis, risk, and prognosis.[18,19] As new diagnoses are made and established diagnoses are modified, aliquots of the biospecimens from clinical archives not only aid in establishing new diagnoses and diagnostic categories, but also provide information as to associations of biomarkers with the severity of disease and with outcomes of diseases.

Most important in the archival collections are biospecimens that are unlikely to be found in bioresources, especially in frozen collections. These are biospecimens that are required for diagnosis and hence, usually are not provided to bioresources. Such specimens include *in situ* carcinomas; treatment naive biospecimens before neoadjuvant therapy; small and large metastases to lymph nodes, brain, liver, and lung; and biopsies of organs with diseases usually not treated by surgery such as small cell undifferentiated

carcinoma of the lung. Other small biopsies, including those of kidney, liver, and lung, will be needed in future research on non-neoplastic diseases for which tissues frequently may not be removed at surgery.[14,15,36,37]

Under pathology oversight and management, aliquots of these biospecimens can be made available to support research even before the 10-year maintenance requirement as long as adequate diagnostic material remains for future study. Many bioresources have agreements with pathology laboratories to supply limited aliquots of these biospecimens to support research of their investigators. The clinical archival tissue model is efficient in the sense that it makes use of biospecimens that are otherwise collected for clinical purposes and for which clinical data typically are readily available through the electronic medical record.[36] However, paraffin-embedded biospecimens from the archives may not be suitable for some types of analyses (e.g., single cell studies).

Some molecules (e.g., RNA) are negatively affected by fixation in 10% NBF and so less RNA can be extracted from FFPE blocks than fresh or frozen biospecimens. Depending on the size of the lesion in an FFPE block, these may or may not be large enough to yield adequate extracted RNA for gene sequencing; however, adequate amounts usually are available for measurements of specific mRNAs using real-time quantitative reverse transcriptase/polymerase chain reaction.[14,15,36] Also, there may be loss of immunorecognition in FFPE tissue on long-term storage[39,40] so research should consider matching biospecimens and results based on the ages of the FFPE blocks utilized.

Clinical Trials Model

The clinical trials model is based on acquiring biospecimens obtained and associated with one or more clinical trials. It is typically project centric. The biospecimens obtained during a clinical trial are used, in part, to aid in the evaluation of the clinical trial; for example, the biospecimens may have been used to monitor some types of responses of biospecimens to a specific therapy. Frequently, the remaining biospecimens obtained during the clinical trial are banked and reserved for future use to evaluate specific effects of the therapy or device under study, but the biospecimens may be used or distributed for other purposes. Frequently, a clinical trial bioresource is controlled and maintained by the pharmaceutical entity that sponsored the clinical trial. Of note, if a clinical trial is unsuccessful, many of the biospecimens collected probably will not be used.

Some biospecimens from bioresources using the clinical trials model may not be useful for some types of other research because the clinical therapy or device may affect the molecular features of the biospecimens in unanticipated ways so that only biospecimens collected from patients with placebo treatments may be useful in future research. This issue is similar to biospecimens acquired after neoadjuvant or adjuvant therapy in other biobanking models.[14,15] Also, unless carefully considered in advance, the informed consents for future undefined use of the biospecimens collected in a clinical trial may not support utilization of the biospecimens in other types of research; however, if the consent is very general, it may be possible to use the biospecimens in other studies, if permitted by relevant regulations and institutional policies. Thus, the goal of the clinical trial biorepository is generally to maintain an inventory to support future research on the therapeutic approach or device under study in the clinical trial.

Of importance, the clinical documentation of the biospecimens may be much more extensive than available from a typical electronic medical record. In a clinical trial biobank, biospecimens may not be fully utilized because many clinical trial bioresources are not designed to support general areas of research and the pharmaceutical bioresource may not release them for other research.

Advocate Model

An advocate model, which is biospecimen centric, typically is developed by organizations that want to increase the study of relatively uncommon diseases or to increase the availability of specific types of biospecimens that are thought to be needed to study a more common disease process. Usually this is a biospecimen-centric model similar to the classic biobanking model. For example, patients without breast cancer, especially those with familial histories of breast cancer, have been asked to donate normal or at-risk breast tissue for future studies (i.e., Susan G. Komen Tissue Bank of the Indiana University Simon Cancer Center).[41]

With infrequent diseases, biospecimens are typically removed at many different medical sites so there may be no efficient approach for a single investigator to obtain enough samples needed to study a specific uncommon or rare disease. In contrast, an advocate organization focused on a rare disease can establish a bioresource and encourage patients with or at risk for the disease to provide remnant tissue to one specific bioresource or several bioresources, which may work together to distribute these uncommon/rare biospecimens for research. For example, because many children's cancers are uncommon, to effectively conduct clinical trials in the United States of America, a single Children's Oncology Group was formed with centralized biobanking under the National Cancer Institute National Clinical Trials Network. This is an excellent approach to ensure the availability of biospecimens to study such diseases and increase tissue utilization.

An example of an advocate biobank is the biobank established to study chordomas (Chordoma Foundation Biobank).[42] Also, a biobank to study hepato/renal fibrocystic diseases is a core of The University of Alabama at Birmingham Hepato/Renal Fibrocystic Disease Core Center.[43]

Uncommon diseases are not frequently studied; thus, advocate organizations, in addition to establishing bioresources, should frequently identify and recruit investigators to utilize the biospecimens they have collected. These biobanks also must aggressively advertise and market their existence. Access to advocate biobanks usually is identified through search engines such as Google or Bing.

Storage Model

A storage model is frequently used by commercial, governmental (national, state, and local), and academic institutions for storage of biospecimens. Typically, in such a model, biospecimens are neither collected by nor independently distributed by the bioresource. Their operations usually are to acquire biospecimens from specific designated entities that have collected the biospecimens. The biospecimens may be processed to aliquots before being sent to the

site of storage. In this model, the control of biospecimens with respect to distribution, to continued storage, or to destruction is usually under the purview of the organization that pays for their storage; this frequently is a governmental entity such as one of the National Institutes of Health (NIH).

With the storage model, the biospecimens may be very underutilized unless the collections are actively marketed and the biospecimens stored in them are well organized and tracked so that the biospecimens can be readily retrieved or discarded. If biospecimens are not well organized in the biorepository (e.g., are intermixed in boxes without association with specific biospecimens or research projects), sometimes, it may be less expensive to continue to store these biospecimens than to discard them.

A potential problem with the storage model is that the distribution of biospecimens stored in them can be limited if they become ''out of sight, out of mind'' and efforts are not made to aggressively market them. Some NIH institutes, which use the model, have encouraged the utilization of biospecimens by requesting grant applications that will use biospecimens from their collections. To optimize biospecimen utilization, there needs to be active marketing, research performed as to the quality of the stored biospecimens, research to identify potential successful uses of such biospecimens, but most important, a very efficient and simple procedure for distributing these biospecimens to investigators without complex or overly burdensome access policies and procedures.

Virtual Model

The virtual model is a diffuse and growing group of multiple subtypes of other models. They tend to be investigator centric, biospecimen centric, project centric, and/or data centric. The simplest virtual bioresource is a group of relatively independent bioresources that act as a single entity with respect to sharing requests for biospecimens, the costs associated with some common activities, and a plan for biospecimen distribution. The CHTN operates as a virtual model composed of bioresources that use the prospective model by sharing requests for tissue; all divisions also contribute to the operations of a central office and informatics support; and there is a common procedure manual.[8] HUB organizations linking various types of bioresources also are being developed to facilitate overall operations.[44]

Other organizations that operate as a virtual bioresource are commercial companies that obtain biospecimens from bioresources and institutions and arrange for distribution of the biospecimens to commercial companies or to investigators (i.e., fulfilling the role of ''middlemen'' in facilitating biospecimen distribution).[11] These types of virtual bioresources have value by increasing biospecimen utilization through the sharing of research requests and resources, as well as using extensive marketing, and aggressive matchmaking between biospecimens and the investigators who need them.

Some nonprofit organizations act as virtual bioresources by providing biobanking-related services and data on the web ranging from central search engines that collect and provide data from numerous tissue-related studies, such as Oncomine, to posting two-dimensional and three-dimensional images from various biospecimens (e.g., The Virtual Biobank, The University of Newcastle, NSW, Australia).[45–49] Because all data are online, biospecimen utilization may be high.

Categories and services that fall within the definition of virtual bioresources continue to expand rapidly with multiple new examples that fall outside the functions of more typical models of bioresources. The virtual model is rapidly becoming a model that supports a wide range of activities related to biospecimens. Of note, many online search services such as Oncomine have proven to be very useful to the scientific community.

Research Consortium Model

The research consortium model has developed based on consortiums that have utilized a large number of biospecimens to support a specific research focus. The model is project specific as well as biospecimen centric. The model develops because funding agencies sometimes may have included a requirement to make unused biospecimens available to investigations in the future both inside and outside the consortium; such a requirement is made independent of whether the unused biospecimens will actually be useful to independent investigators and hence, requested. To meet this requirement, a bioresource might be established to support such biospecimen availability. An example of such a consortium in which many biospecimens are in storage is the GTEx protocol in which large numbers of organ donor biospecimens were collected and analyzed as to the quality of RNA in biospecimens from human organ donations and from other human biospecimens.[49,50]

While some of these consortiums may establish bioresources for sharing biospecimens and data with investigators performing secondary research, the establishment of such bioresources was not usually the primary goal of the consortiums. In such cases, aggressive marketing is needed to ensure minimal and/or optimal utilization of these biospecimens; if inadequate independent utilization occurs over the first 2 years, <10% of the inventory, closing of the bioresources probably should be considered to avoid unnecessary expenses, unless continued existence is justified by the project. In addition, before a requirement to establish a bioresource is made, the cost effectiveness for adequate utilization of the selected biospecimens should be justified by the funding agency. Because operations of any bioresource is expensive, this requires a thorough review by individuals who have operational experience in biorepository operations.

Unnamed Model

The ''unnamed model'' falls under the most general description of a bioresource; specifically, any entity that collects, processes, stabilizes, stores, and/or distributes biospecimens. ''Unnamed bioresources'' typically may not be recognized as formal bioresources by their developers and/or users. These bioresources tend to develop gradually, probably due to lack of adequate funding; they are unnamed and may not correspond to specific biobanking models, but tend to be project and/or biospecimen centric.

Rather than a planned approach to developing a bioresource, an unnamed bioresource may develop based on a developer's interest in specific biospecimens, in a disease process, and/or in an experimental question. Typically, there

are no plans for long-term operations and/or to the utilization of a large proportion of their biospecimens. These bioresources tend to be relatively small with limited funding and with usually only one or two personnel aiding in their operation. Frequently, they may support only one research area (e.g., pancreatic cancer) or even one research project (e.g., novel hormonal therapies for breast cancer).

An unnamed bioresource may be disorganized and not meet any of the best practices recommended by ISBER or other best practices.[5–7] The biospecimens may be collected through a ''catch-as-catch-can'' approach. For example, sometimes biospecimens that are considered to be somewhat interesting are put in a freezer with inadequate labeling and/or a record as to where in the freezer the biospecimen is located. There may not be information on the patient source, labels may be incorrect, inadequate, unreadable, or absent. There may be no quality management system (QMS) nor QC on such biospecimens and if they are linked to a surgical pathology report, no additional information on the specific biospecimen aliquot stored, including the extent of tumor involvement, necrosis, fibrosis, mucin, inflammation, and/or the presence of uninvolved tissue in the biospecimen, are documented. Most such biospecimens may not be very useful, especially for high-quality studies.

In working with unnamed biobanks, we have observed problematic labeling of biospecimens, plus there may be no QC by a pathologist of aliquots provided to an investigator. When these problems occur, the error rates as to correct diagnoses of the biospecimens are usually 40% or higher. In addition, the unnamed bioresource may operate without approval by an ethics review board. Thus, using biospecimens from an unnamed biobank should be approached with caution. Biospecimens from an unnamed bioresource may be a great resource or cause a great deal of headaches unless adequate attention is given to following best practices for biospecimen handling and the required ethics review board approvals are obtained.

In our experience, based on using biospecimens experimentally from unnamed biobanks, the quality of these biospecimens may be quite variable. Nevertheless, some of these bioresources may be important to biomedical research in that high-quality biospecimens may be collected, processed, stabilized, stored, and distributed to investigators by utilizing SOPs, QC of the biospecimens, and an overall quality management system. Some of these bioresources have aided investigators by collecting an independent donor cohort from whom high-quality biospecimens can be provided to an investigator to verify biomarkers of risk, diagnosis, or prognosis.

Summary and Conclusions

Multiple biobanking models have been developed to support research through the distribution of human biospecimens or associated components and/or data. Each of the models typically have a focus that may be investigator centric, biospecimen centric, population centric, data centric, or project centric. The appropriate choice and use of the models may facilitate the utilization of biospecimens in research or the provision of data obtained from biospecimens. There is no perfect biobanking model. Each model has both advantages and disadvantages; the choice of model should be based on the nature of the research that the biospecimens of the model are intended to support, as well as the forecasted needs for biospecimens of researchers and sponsors. To ensure optimal biospecimen utilization, before a new bioresource is established, careful consideration should be given to the choice of the biobanking model, its goals, design, and management; the bioresource's intended customers/investigators; and tissue utilization.[8,9] The selection of a biobanking model by a bioresource does not ensure adequate tissue utilization; this is facilitated by the goals, design, management, and operations which will vary among bioresources selecting the same model. In addition to the primary model, the design of the bioresource may include components of other models. This is usually necessary for efficiency, such as including prospective collections of viable biospecimens in a classic biobanking model. Each bioresource using the same primary model may have variable designs, different goals, and approaches to operations.

Several issues are emphasized that may increase the availability and utilization of biospecimens. These include a design which incorporates a plan for tissue utilization and active marketing approaches, such as an online inventory of available biospecimens to aid investigators in finding the biospecimens their studies require. Also, utilization is improved when bioresources frequently monitor the balance among inventory, biospecimen collection, and biospecimen distribution.

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