

Biobanking on a Small Scale: Practical Considerations of Establishing a Single-Researcher Biobank

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Abstract

In this paper, practical issues of biobanking within the context of a single, relatively small project are considered. Definitions of biobanking assume the collection and storage of samples for later analysis under conditions that permit efficient retrieval and optimum sample stability. No requirements on sample size or number of studies are imposed in the definitions of biobanks. Correspondingly, a single laboratory can establish and maintain a biobank. Regardless of size and intention, a single investigator establishing a biobank faces a number of issues, including obtaining IRB approvals, developing strategies for specimen collection and optimal storage, and negotiating such issues as (1) response rates; (2) biobank size; (3) various sampling biases; (4) establishing safeguards against sample duplication and overlap with other biobanks; and (5) securing resources for sample processing and maintenance. This paper will review and comment on all of these considerations.

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I. INTRODUCTION

Rapid development of genetic and genomic sciences has generated a number of unresolved and minimally explored ethical and legal questions. Among these questions are those pertaining to how to organize collections of specimens for genetic and genomic research. Most of the contributions concerning biobanks explore such questions in the context of establishing large-scale biobanks. These biobanks typically involve multiple investigators, ethics professionals, and lawyers working together. Here we focus on issues that are faced by a single investigator who is trying to independently establish a biobank. In fact, whether the investigator calls it a biobank or a mini-collection, the regulations discussed here will apply. Specifically, we discuss a number of considerations that are important at various stages of designing, establishing, maintaining, and destroying a biobank. Ultimately, we argue that such biobanking on a small scale is as important to the development of the genetic and genomic sciences as large-scale efforts, and that issues pertaining to small-scale biobanking should be considered and studied by universities and authorities in research with human subjects with the same degree of engagement with which they approach issues of large-scale biobanking.

II. DEFINITIONS OF BIOBANKS

Since the completion of the first draft of the human genome, the genetic, medical, and behavioral sciences have experienced substantial and rapid development in technology and methodology, allowing exploration and analysis of various aspects of genome structure and function. In conjunction with these advancements, research conducted during the first years of this century brought about a realization of the inherent heterogeneity of the human samples collected for purposes of genetic and medical research, raising difficulties in interpreting results.¹ Hence, the need to control for this heterogeneity arises. Controlling for heterogeneity requires either establishing very large sample collections from particular, well-defined cohorts of individuals² or minimizing heterogeneity by working with distinctly homogeneous groups of people.³ Homogeneity may be determined by genetic factors, such as distinct ethnic or familial background,⁴ or by environmental factors, such as exposure to radiation.⁵ Regardless of the source of homogeneity in a research population, all genetic research will require obtaining large

¹ E.g., Nicole C. Allen et al., *Systematic Meta-analyses and Field Synopsis of Genetic Association Studies in Schizophrenia: the SzGene Database*, 40 NATURE GENETICS 827, 831 (2008); Lars Bertram et al., *Systematic Meta-analyses of Alzheimer Disease Genetic Association Studies: the AlzGene Database*, 39 NATURE GENETICS 17, 21 (2007).

² Lyle J. Palmer & Lon R. Cardon, *Shaking the Tree: Mapping Complex Disease Genes with Linkage Disequilibrium*, 366 LANCET 1223, 1228, 1229, 1231 (2005).

³ Peter Henneman et al., *Prevalence and Heritability of the Metabolic Syndrome and its Individual Components in a Dutch Isolate: The Erasmus Rucphen Family Study*, 45 J. MED. GENETICS 572, 572, 574 (2008).

⁴ Bertis B. Little, Robert M. Malina, & Maria E. Reyes, *Natural Selection and Demographic Transition in a Zapotec-Speaking Genetic Isolate in the Valley of Oaxaca, Southern Mexico*, 35 ANNALS HUM. BIOLOGY 34, 37 (2008).

⁵ Klara Muksinova et al., *A Repository of Bio-specimens from Mayak Workers Exposed to Protracted Radiation*, 90 HEALTH PHYSICS 263, 263 (2006).

numbers of biological samples. The developments in our understanding of the influence of heterogeneity have only increased the number of samples that researchers must collect so that they may control for exogenous variation. Hence, one of the outcomes of this realization of heterogeneity has been the establishment of biobanks, or collections of biological specimens. These repositories are built to (1) ensure that sufficient sample sizes are drawn from the general population so that their power may allow researchers to overcome the impact of heterogeneity statistically; and (2) capitalize on the homogeneity of carefully ascertained, but often limited, collections so that these collections' purity can aid in the initial identification of genetic mechanisms..

Today biobanking—the process of collecting, maintaining, and sharing biological samples—is viewed as an essential tool in the modern landscape of the genetic, medical, and behavioral sciences.⁶ The literature also contains various definitions of what constitutes a biobank. For example, Lee refers to a biobank as a collection of specimens that have a secure funding source, a cryogenic storage facility, developed criteria for the selection of the best samples to be stored, ongoing research with these samples, and continuing improvement of sample collection/processing and storage conditions.⁷ In other sources, biobanks are referred to as large repositories of biospecimens that are supplemented with clinical data and they are viewed as a means to merge two major trends in biomedical research, one pertaining to the capacity to generate and handle huge amounts of biological (e.g., genomic and proteomic) data, and the second one related to the accumulation, electronic storage, and integration of patient clinical records.⁸ During the last decade or so, with mushrooming numbers of biobanks, modern requirements for them have added robust bioinformatics systems, and mechanisms of compliance with various regulations pertaining to research with human subjects.⁹

Currently there are many ongoing biobanking efforts to collect tissue and DNA both nationally¹⁰ and around the world.¹¹ These efforts vary tremendously, from those collecting from entire nations, such as the national repositories in Iceland¹² and Estonia¹³,

⁶ E.g., Paolo De Paoli, *Biobanking in Microbiology: From Sample Collection to Epidemiology, Diagnosis and Research*, 29 FED'N EUR. MICROBIOLOGICAL SOC'Y MICROBIOLOGY REV. 897, 898 (2005).

⁷ Robert E. Lee, *Environmental Specimen Banking: A Complement to Environmental Monitoring*, in BIOLOGICAL TRACE ELEMENTS RESEARCH 321-27, at 321 (G.N. Schrauzer ed., 1990).

⁸ BioBank Central – About Us, http://www.biobankcentral.org/about/fc_bc.php (last visited Mar. 25, 2009).

⁹ Laura M. Beskow et al., *Informed Consent for Population Based Research Involving Genetics*, 286 J. AM. MED. ASS'N. 2315, 2317, 2321 (2001).

¹⁰ E.g., Katrina Gwinn et al., *Amyotrophic Lateral Sclerosis: An Emerging Era of Collaborative Gene Discovery*, 2 PUB. LIBR. SCI. ONE e1245, 1 (2007).

¹¹ E.g., Susan M.C. Gibbons et al., *Lessons from European Population Genetic Databases: Comparing the Law in Estonia, Iceland, Sweden and the United Kingdom*, 12 EUR. J. HEALTH L. 103, 103 (2005); Lea Tenenholz Grinberg et al., *Brain Bank of the Brazilian Aging Brain Study Group—A Milestone Reached and More Than 1,600 Collected Brains*, 8 CELL TISSUE BANKING 151, 151 (2007); Susanne B. Haga & Laura M. Beskow, *Ethical, Legal, and Social Implications of Biobanks for Genetics Research*, 60 ADVANCES IN GENETICS 505, 506 (2008); Maria J. Molnar & Peter Bencsik, *Establishing a Neurological-Psychiatric Biobank: Banking, Informatics, Ethics*, 244 CELLULAR IMMUNOLOGY 101, 101 (2006); Manuel M. Morente, Enrique de Alava, & Pedro L. Fernandez, *Tumour Banking: The Spanish Design*, 74 PATHOBIOLOGY 245, 245 (2007); Klara Muksinova et al., *supra* note 5, at 263.

¹² Jon F. Merz, Glenn E. McGee, & Pamela Sankar, *"Iceland Inc."?: On the Ethics of Commercial Population Genomics*, 58 SOC. SCI. & MED. 1201, 1201 (2004).

¹³ Amy L. Fletcher, *Field of Genes: The Politics of Science and Identity in the Estonian Genome Project*, 23 NEW GENETICS & SOC'Y 3, 3 (2004).

to collections focused on well defined ethnic, cultural, or religious subgroups;¹⁴ from people affected with common genetic disorders and diseases¹⁵ (e.g., NUgene Project,¹⁶ the Personalized Medicine Research Project [PMRP]¹⁷) to normative samples of volunteers;¹⁸ and from approaches to sample collection and storage that assume de-identification¹⁹ to those that assume complete identifiability, such as the Environmental Polymorphisms Registry (EPR).²⁰ The establishment and maintenance of these banks has generated considerable discussion in the literature about the legal, medical, ethical and research issues related to biobanks.²¹

What is underrepresented in the literature is a discussion of the issues involved in establishing a biobank on a “small scale.” Most small biobanks pertain to particular well-characterized collections from groups of a limited size, such as collections of specific ethnic groups or particular families; of a particular subcondition, such as a particular subtype of a particular disorder; or a particular environmental exposure, such as specimens from children of individuals exposed to a particular environmental condition such as famine. These small biobanks are typically established by a single investigator and maintained by a single laboratory. Here, we explore a number of issues pertaining to such biobanking on a small scale.

III. “DESIGNING” A BIOBANK

A single-investigator/single-lab biobank is typically established for a particular project. While designing such a project, an investigator has an opportunity and a responsibility to (1) determine that the population/sample in question with which the investigator works can and should be used for biobanking purposes; (2) convince the funder of the necessity of biobanking, since banking, by definition, is more expensive than establishing a sample for limited use; and (3) design the procedures for specimen collection and biobanking that take into account the relevant observations in the literature. These procedures differ on a number of parameters. Here we consider three differences that are relevant to this discussion.

The first and most obvious difference is *what* types of specimens are collected (e.g., saliva, whole blood, tissue). The type of specimen is determined by the nature of

¹⁴ E.g., Elizabeth A. Streeten et al., *Autosome-Wide Linkage Analysis of Hip Structural Phenotypes in the Old Order Amish*, 43 *BONE* 607, 607 (2008).

¹⁵ See Mike Mitka, *Banking on Genes, DNA Sought as Key to Disease Causes and Cures*, 288 *J. AM. MED. ASS'N* 2951, 2951 (2002).

¹⁶ The NuGene Project Home Page, <http://www.nugene.org/> (last visited Jan. 15, 2009).

¹⁷ Personalized Medicine Research Project Home Page, <http://www.marshfieldclinic.org/pmrp> (last visited Jan. 15, 2009).

¹⁸ E.g., Geraldine M. McQuillan, Qiyuan Pan, & Kathryn S. Porter, *Consent for Genetic Research in a General Population: An Update on the National Health and Nutrition Examination Survey Experience*, 8 *GENETICS MED.* 354, 354 (2006).

¹⁹ E.g., Rajiv Dhir et al., *A Multidisciplinary Approach to Honest Broker Services for Tissue Banks and Clinical Data: A Pragmatic and Practical Model*, 113 *CANCER* 1705, 1705 (2008).

²⁰ Patricia C. Chulada et al., *The Environmental Polymorphisms Registry: A DNA Resource to Study Genetic Susceptibility Loci*, 123 *HUM. GENETICS* 207, 207 (2008).

²¹ A. Cambon-Thomsen et al., *Trends in Ethical and Legal Frameworks for the Use of Human Biobanks*, 30 *EUROPEAN RESPIRATORY J.* 373, (2007); Manuel M. Morente, Pedro L. Fernandez, & Enrique de Alava, *Biobanking: Old Activity or Young Discipline?* 25 *SEMINARS DIAGNOSTIC PATHOLOGY* 317, 317 (2008).

the project under which the collection is to be conducted. For example, the “storability” and “usability” properties of DNA have been reported to be different when extracted from saliva, fresh whole blood, or transformed cells (cell lines).²² Depending on the goals of the project and its corresponding requirements for DNA properties, the investigators should make proper decisions about what specimens need to be collected. This decision will need to be reflected in the corresponding consent documents.²³

The second relevant parameter, closely related to the types of specimens to be collected, is *how* the collected specimens will be handled, including processing, maintenance, and storage. For example, if saliva is collected via cytobrushes, the DNA should be extracted as soon as possible.²⁴ Extracted DNA can be stored at -80°C, whereas transformed cells should be stored at much lower temperatures, in liquid nitrogen. Similarly, tissues from different organs which are sampled at different times, require different procedures for RNA extraction and storage.²⁵ All of these details determine the costs associated with specimen collection and banking.

The third parameter is how to account for considerations that arise from the *size* of the biobank. For example, a single-lab/single-investigator bank typically contains a relatively small number of specimens, but these specimens are likely to be donated by well-characterized individuals from distinct samples or populations. Small biobanks are also likely to have multiple types of specimens, such as blood and tissue.

It is important, in designing a biobank and setting these three parameters, to consider the possible issues that might arise in the process of data collection, storage, and sharing, and, thus, might characterize the biobank. Participation bias during data collection is one such issue that can alter the character of a biobank by changing its generalizability (if, for example, only individuals of Caucasian background donate their specimens) and, correspondingly, its usability (if, for example, the overall goal is to generate a drug that can be used by the majority of the general population in the United States).²⁶

A. Rates of Consenting, Donating, and Withdrawal

Overall rates of consenting for biobanking are highly variable, ranging from 98.4%²⁷ to 84.8%.²⁸ These rates vary widely depending on the nature of the sample—general population vs. clinical population; whether the consent form guarantees de-

²² E.g., Sara M. Beckett et al., *Buccal Swabs and Treated Cards: Methodological Considerations for Molecular Epidemiologic Studies Examining Pediatric Populations*, 167 AM. J. EPIDEMIOLOGY 1260, 1260 (2008); James M. Swanson, et al., *Effects of Source of DNA on Genotyping Success Rates and Allele Percentages in the Preschoolers with Attention-Deficit/Hyperactivity Disorder Treatment Study (PATS)*, 17 J. CHILD ADOLESCENT PSYCHOPHARMACOLOGY 635, 635 (2008); Thomas V. Hansen et al., *Collection of Blood, Saliva, and Buccal Cell Samples in a Pilot Study on the Danish Nurse Cohort: Comparison of the Response Rate and Quality of Genomic DNA*, 16 CANCER EPIDEMIOLOGY BIOMARKERS & PREVENTION 2072, 2072 (2007).

²³ See 45 C.F.R. § 46.116 (West 2009).

²⁴ See Beckett, *supra* note 22, at 1262.

²⁵ E.g., Johanna M. Beekman et al., *Recovery of Microarray-quality RNA from Frozen EDTA Blood Samples* 59 J. PHARMACOLOGICAL TOXICOLOGICAL METHODS 44, 44 (2009).

²⁶ Lisa DiMartino et al., *Characteristics Associated with Participation in DNA Banking: The National Registry of Veterans with ALS*, 28 CONTEMP. CLINICAL TRIALS 572, 572 (2007).

²⁷ McQuillan et al., *supra* note 18, at 357.

²⁸ *Id.*

identification or not; the way the study is presented to potential participants; whether the individual attempting to obtain the consent is a treating physician, other practitioner, or researcher; and many other factors. Adding to the variability, typically, only a portion of the individuals who consent to donate specimens actually donate them. Again, the published figures vary widely, ranging from 100%²⁹ to ~75%.³⁰ Finally, participants may withdraw after donation, with stated rates of ~.5%³¹ withdrawing almost immediately after donating the specimens, and of ~1%³² when participants were recontacted for various purposes some time after the donations were made. Accordingly, when establishing a biobank, researchers should take these data into account, anticipating that only a certain percentage of their approached participants will ultimately donate specimens for biobanking.

B. Representation of Participant Subgroups

It appears that the decision to donate is not made equiproportionally among various subgroups. In particular, individuals of European descent consent to donate DNA specimens for biobanking purposes at higher rates than individuals of minority backgrounds.³³ Men consent more frequently than women.³⁴ Participants in clinical studies appear to donate more readily than healthy individuals.³⁵ Donations of saliva are made more easily than donations of whole blood.³⁶ In addition, the literature is replete with, at this point, rather idiosyncratic but noticeable observations, such as the differential rates of donations among smokers and nonsmokers,³⁷ patients with varying severities of a condition,³⁸ married and single individuals,³⁹ and many other groupings.

C. Sample Storage

Yet another consideration that is crucially important for the establishment and proper functioning of a biobank is sample storage. Much literature is dedicated to this purpose, and here we highlight only selected aspects. Biobanks should be characterized as having high-quality specimens stored in them, easy specimen retrieval, accessible information characterizing the sample as fully as possible, and security to prevent any “third party” from identifying the sample.⁴⁰ This last consideration is particularly

²⁹ *Id.* at 357.

³⁰ Chulada et al., *supra* note 20, at 209.

³¹ *See id.* at 210.

³² *See id.* at 210.

³³ DiMartino et al., *supra* note 26, at 575; Geraldine M. McQuillan et al., *supra* note 18, at 357-58.

³⁴ McQuillan et al., *supra* note 18, at 358. *But see*, Lisa DiMartino et al., *supra* note 26, at 575.]

³⁵ Gwinn et al., *supra* note 11, at 4.

³⁶ Maria T. Landi & Neil Caporaso, *Sample Collection, Processing and Storage*, 142 INT'L AGENCY RES. ON CANCER SCI. PUBLICATIONS 223, 223 (1997).

³⁷ Kjersti Aagaard-Tillery et al., *Sample Bias Among Women with Retained DNA Samples for Future Genetic Studies*, 108 OBSTETRICS & GYNECOLOGY 1115, 1115 (2006).

³⁸ DiMartino et al., *supra* note 26, at 575.

³⁹ Kjersti Aagaard-Tillery et al., *supra* note 37, at 1117-1118.

⁴⁰ A. Jamie Cuticchia et al., *NIDDK Data Repository: A Central Collection of Clinical Trial Data*, 6 BIOMED CENT. MED. INFORMATICS & DECISION MAKING 19, 19 (2006); Sharon F. Terry & Patrick F. Terry, *A Consumer Perspective on Forensic DNA Banking*, 34 J.L., MED. & ETHICS 408, 408 (2006); Melissa Thornton et al., *Automation and Validation of DNA-banking Systems*, 10 DRUG DISCOVERY TODAY 1369, 1369 (2005).

important for establishing biobanks involving vulnerable populations, such as those who are unable to consent independently, including, children younger than 18 and the mentally ill, and those who consent under special circumstances, such as while in detention, and is discussed below.⁴¹

D. Data Sharing

The final consideration that we want to mention in this section is the critical importance of data sharing. The very idea behind biobanking is to establish a resource that is bigger than a single project or a single laboratory. In contrast to the rapid development of the technology that has resulted in data-generation on already-available specimens that is speedier, easier, and cheaper, the collection of biospecimens remains difficult, and is possibly getting more difficult than ever before.⁴² Biobanks, which are essential for any kind of exploration in human genetics, are, correspondingly, becoming more central to discovery and more precious to those who establish, maintain, and work with them. Small biobanks that typically contain unique collections of specimens that cannot be easily replaced or replicated at all are particularly important. In light of both the increased significance of biobanks for new discoveries and the increased difficulty related to the collection of specimens, sharing banked samples is an essential feature of biobanking. Four aspects of sharing banked materials are discussed here: (1) making the decision to share considering limited amounts of the biomaterials to share and the necessary resources to do so; (2) tracking the samples to be shared and preparing a subsample/sample for sharing; (3) sharing all of the necessary information on the phenotypic characterization of a participant; and (4) tracking the samples that are engaged in different studies.

The decision to share banked samples should be governed by the interests of science, the interests of the participants who donated to the bank, and the interests of the organization/structure that have invested in the development of the bank. In large biobanks, most of these decisions are guarded by a board of some kind that oversees the functioning of the bank.⁴³ However, while the formation of such boards is common practice for large banks, a small one-lab bank, most likely, will not have a governing board. Correspondingly, it is up to the investigator to make decisions about sharing. Yet, although a researcher is typically fully able to make such a decision, it is advisable to engage another party in the decision-making process. Such a collective engagement might be instrumental in (1) ensuring that the decision to share/not share is made conscientiously; (2) avoiding possible legal actions, if such could arise;⁴⁴ and (3) ensuring that the biobank has enough materials in it left to continue to be considered a biobank.

⁴¹Currently, the discussion of these issues is limited in the literature, but there are some relevant publications, e.g., Adrian Smith, *Disaster Victim Identification of Military Aircrew 1945-2002*, 74 AVIATION SPACE & ENVTL. MED. 1198, 1198 (2003); Terry & Terry, *supra* note 40, at 408, 413.

⁴²Morente et al., *supra* note 21, at 319-320.

⁴³E.g., Catherine A. McCarty et al., *Community Consultation and Communication for a Population-based DNA Biobank: The Marshfield Clinic Personalized Medicine Research Project*, 146A AM. J. MED. GENETICS 3026, 3026 (2008); Richard Tutton, Jane Kaye, & Klaus Hoeyer, *Governing UK Biobank: The Importance of Ensuring Public Trust*, 22 TRENDS BIOTECHNOLOGY 284, 284 (2004).

⁴⁴See *infra* p. 13.

Taking samples and preparing a subsample for sharing can be done by using one of the many models that permit automatized tracking and quick retrieval of all samples.⁴⁵ These systems have been developed for large-scale biobanking, but any single investigator can model off these systems effectively. Although the scale of banking would be different, many of the elements of automatized guarding of the samples might be effective.

The researcher must also decide what other, nongenetic data to share about the samples. At one extreme, all samples released by the bank would be accompanied by a comprehensive set of nongenetic characteristics. Researchers and IRBs⁴⁶ vary in their preference with regard to how much information on the sample should be available. There are interpretations of answers to this question: a researcher might decide to organize this release in a number of ways, ranging from releasing a limited selected set of information to releasing all of the information.

Last but not least, it is important to acknowledge that there is a concern that if some biobanks permit access to their banks indiscreetly, whole samples or large groups of participants might end up in multiple overlapping samples. Clearly, it is highly desirable to attempt the tracking of specimens from publication to publication. Thus, it is essential that the biobank itself monitors or oversees the projects to which its samples are directed.

VI. NAVIGATING THE INSTITUTIONAL REVIEW BOARD (IRB)

The IRB has oversight responsibilities under the Common Rule whenever research involves the collection of identifiable private information for research purposes.⁴⁷ Collection of biological specimens and the related descriptive data necessitates obtaining IRB approval for development of the biobank.⁴⁸ If the specimens are retained with identifiers, the IRB is required to maintain oversight of the storage and subsequent distribution of the identified specimens.⁴⁹ Creating and maintaining a biobank thus can be thought of as a two-step process requiring: (1) collection of the specimens; and (2) maintenance and distribution of the specimens. Different concerns arise for the IRB in the two steps as described below.

A. Collection of Samples

The main issue for the IRB regarding collection of biological specimens relates to obtaining appropriate consent for both the main study itself as well as for the indefinite storage of the participant's biological specimen(s). Along with the standard consent requirements,⁵⁰ consent for banking specimens requires particular attention to informing participants (1) that they may decline to have their specimens stored without altering their ability to participate in the current research even when the current research involves specimen collection; (2) about the types of research for which their specimens may be

⁴⁵ See Thornton et al., *supra* note 40, at 1374.

⁴⁶ See *infra* p. 10 for a discussion of IRB concerns related to release of information.

⁴⁷ See 45 C.F.R. § 46.101(a) (West 2009).

⁴⁸ 45 C.F.R. §46.102(f) defines the term human subjects to include not only interaction with individuals but also the collection of identifiable private information.

⁴⁹ DHHS Office of Human Research Protections, Issues to Consider in the Research Use of Stored Data or Tissues (1997), available at <http://www.hhs.gov/ohrp/humansubjects/guidance/reposit.htm>.

⁵⁰ 45 C.F.R. § 46.116.

used; (3) whether they will have the option to have their specimen(s) destroyed at a later time, anonymized, or otherwise constrain research use; and (4) whether they may be re-contacted for consent prior to any future use of the specimens. Careful attention to these issues up front will minimize problems managing the biobank. For example, advising participants that they may request to have their specimen(s) destroyed is only feasible if the specimens remain identified.

As a practical matter, obtaining informed consent for both collection and banking can be a complicated matter. Along with consent for these two activities, investigators subject to the Privacy Rule of the Health Insurance Portability and Accountability Act (“HIPAA”) also must obtain a HIPAA authorization for both activities.⁵¹ HIPAA is intended to ensure that patients and research participants are fully informed and maintain autonomy over their information and biological materials. To meet this regulatory intent, HIPAA, unlike the Common Rule, limits the occasions on which multiple authorizations and consents can be combined,⁵² leading to several separate forms containing much redundant information. While investigators and IRBs labor extensively in an effort to make these documents understandable and to pair the documents with verbal presentation of the information, the literature suggests that the degree of understanding achieved by participants is quite low.⁵³ Some IRBs have allowed the consents and authorizations to be combined into a single document, albeit with multiple signatures and/or checkboxes, in an attempt to reduce the need to present redundant information. Whether such an approach improves participant understanding remains to be determined.

B. *Maintenance and Subsequent Use of Biobank Specimens*

Oversight of the biobank by an IRB is only necessary when the biobank includes identifiable information.⁵⁴ Currently, data and samples which are stripped of any identifiers are no longer considered to involve human subjects or to contain protected health information⁵⁵, and hence are no longer subject to either the Common Rule or HIPAA.⁵⁶ Currently, the specimen itself is not considered to be inherently identified. At some future point, the ability to extract genetic material from many biological specimens may render them identifiable. For the moment, however, the confidentiality risks arise because there is scientific need to retain the identifiers or links to identifiers. However, thoroughly de-identifying the data often limits the scientific usefulness of the specimens by precluding the ability to link the specimens to any future data such as mortality rates

⁵¹ 45 C.F.R. § 164.508.

⁵² *Id.*

⁵³ For a recent discussion of patients’ understanding of consent, see generally Victor Schwartz & Paul S. Appelbaum, *Improving the Quality of Informed Consent to Research*, 30IRB ETHICS & HUMAN RESEARCH 19 (2008). For quantification of additional difficulties in recruiting participants following the implementation of HIPAA, see Michael S. Wolf & Charles L. Bennett, *Local Perspective of the Impact of the HIPAA Privacy Rule on Research*, 106 CANCER 474, 477 (2007). Laura M. Beskow & Elizabeth Dean, *Informed Consent for Biorepositories: Assessing Prospective Participants’ Understanding and Opinions*, 17 CANCER EPIDEMIOLOGY BIOMARKERS & PREVENTION 1440, 1442 (2008) provides an analysis of patient understanding specifically in the context of biorepositories.

⁵⁴ See 45 C.F.R. §46.102(f) (2005) for a definition of when research involves human subjects and hence when IRB oversight is required.

⁵⁵ 45 C.F.R. §164.501 defines protected health information as being individually identifiable.

⁵⁶ 45 C.F.R. §164.500.

or recurrence of disease. Investigators are advised to consider the potential need to expand the data set prior to committing to de-identify the specimens.

Assuming that in most cases, the specimens will be maintained with identifiers, the IRB will likely be concerned about the security of the specimens and data.⁵⁷ Along with implementing adequate security plans such as encrypting electronic copies and limiting physical access, investigators should consider whether there is the potential for compelled disclosure. If the information is likely to be of any interest to a United States court and subject to subpoena, a Certificate of Confidentiality should be obtained from the Department of Health and Human Services.⁵⁸ For example, collection of specimens from incarcerated individuals or specimens from a population with a history of illegal activity could be of interest in criminal investigations and benefit from the protection afforded by a Certificate of Confidentiality.

Consent remains an important area of concern during biobank maintenance and at the time of secondary use of the specimens. While all specimens would have entered the biobank with a valid consent, if the specimen donors were minors at the time of collection, they may reach the age of majority during the course of biobank maintenance, raising concern as to whether the initial consent, most likely parental permission, is still valid. IRBs vary as to the need to contact the now adult specimen donor to request consent for continued inclusion in the biobank. If there has been continued contact with the donor, however, it is generally recommended that consent be sought.

Future research using identified banked specimens must comply with the consent requirements of the Common Rule and the authorization requirements of HIPAA, if applicable.⁵⁹ If the nature of secondary research use was not foreseen at the time of specimen collection, donors are not considered to have provided adequate consent and authorization for the research, only consent and authorization to store the specimen.⁶⁰ Both the Common Rule and HIPAA have provisions to allow the IRB to waive the consent and authorization requirements⁶¹ and studies suggest that in many cases, participants are comfortable with an IRB or ethics board allowing such research without consent.⁶² In considering a waiver of consent/authorization, the IRB is likely to consider several key factors including: (1) the feasibility of obtaining participants' consent, which depends on the size of the population and the ability to locate participants if there has been no continued contact; (2) the adequacy of the participants' initial consent to bank the specimen, particularly whether the participants were likely to have understood that their consent included the type of research being subsequently proposed. For the small scale biobank, subsequent use of the samples will most likely involve research in areas

⁵⁷ See 45 C.F.R. § 46.111(7) and 45 C.F.R. § 164.530(c) for Common Rule and Privacy Rule requirements, respectively.

⁵⁸ 42 U.S.C. § 241(d)

⁵⁹ 45 C.F.R. § 46.116 and 45 C.F.R. § 164.508, respectively.

⁶⁰ 45 C.F.R. § 46.116(a)(1) (2005) and 45 C.F.R. § 164(c)(iv) (2002) both require specificity as to the use of the information and/or samples.

⁶¹ 45 C.F.R. § 46.116(d) (2005) and 45 C.F.R. § 164.512(i) (2002), respectively.

⁶² For qualitative studies on research volunteer's opinions on the need for obtaining consent for each secondary use, see Klaus Hoeyer et al., *The Ethics of Research Using Biobanks: Reason to Question the Importance Attributed to Informed Consent*, 165 ARCHIVES OF INTERNAL MED. 97, 99 (2005); David Wendler, *One-Time General Consent for Research on Biological Samples: Is it Compatible with the Health Insurance Portability and Accountability Act?*, 166 ARCHIVES OF INTERNAL MED. 1449, 1451 (2006).

related to the initial research, and hence the participants in most cases anticipate and consent to such related research. Problems arise when the investigator moves to new areas of research or wishes to share samples with a colleague conducting disparate research. If the new research area was not contemplated at the time of specimen donation and is therefore not included in the banking consent, the IRB may not be willing to approve the subsequent use. Investigators can avoid this situation through careful crafting of the initial consent/authorization to be specific while referencing as broad a scope of future research as possible.

That future research is unknowable at the time of specimen collection also precludes predicting what information may be gleaned about participants in the future. In designing research that utilizes existing banked specimens, investigators must consider whether the research may lead to information of relevance to the participants and whether that information should be provided to the specimen donors. While participants are unlikely to be interested in many results, they are interested in findings related to serious health conditions.⁶³ For example, if the research might possibly uncover a genetic predisposition to a treatable disease, should the participants be told this information in the context of research of which they are unaware? Decisions in these cases often depend on the reliability of the results, the magnitude of the disease impact and the ability to treat the newly identified condition or predisposition.

V. CONTROL AND OWNERSHIP OF THE BIOBANK

Several parties have an interest in the biobank specimens, including the investigator and collaborating researchers, the university under whose auspices the specimens are collected and stored, the funding agency, specimen donors, and any interest groups such as the disease advocacy groups or collaborating organizations who facilitated the specimen collection. The interests of these parties have, in a few cases, been considered by the courts as well as the popular press.⁶⁴ Unfortunately, the differences in the details of those cases have led to disparate court responses,⁶⁵ which in turn have resulted in a murky understanding at best of who has control over biobanks.

Most universities consider all data and specimens collected by an investigator with a formal affiliation with that university to be owned by the university.⁶⁶ Such ownership rights are often spelled out in institutional technology transfer offices and patent policies. From the university perspective, funding awards are made to institutions as opposed to individual investigators, vesting the university with both the responsibility

⁶³ See Beskow, *supra* note 54, at 1440, 1445, 1446 (2008) (describing the responses of specimen donors regarding under what circumstances they would like to be contacted in the future regarding research results).

⁶⁴ E.g., Rebecca Skloot, *Body-Stuff Politics*, N.Y. TIMES, Apr. 16, 2006, Magazine, available at http://www.nytimes.com/2006/04/16/magazine/16tissue.html?_r=2&oref=slogin.

⁶⁵ These disparate court decisions are reviewed in Mark Barnes & Kate Gallin Heffernan, *The 'Future Uses' Dilemma: Secondary Uses of Data and Materials by Researchers and Commercial Research Sponsors*, 3 MED. RES. L. & POL'Y REP. 440, 442-3 (2004); Rina Hakimian & David Korn, *Ownership and Use of Tissue Specimens for Research*, 292 J. AM. MED. ASS'N 2500, 2502 (2004).

⁶⁶ C.f. *Washington University v. Catalona*, 490 F. 3d 667 (2007) for a description of the arguments used by one educational institution in favor of university ownership of biospecimens.

for ethical and compliant research as well as ownership of the research product, be it information or specimens.

Federal funding agencies, in most cases, do not claim ownership of an investigator-initiated biobank. This is not necessarily the case for work done under privately funded research contracts, such as oncology cooperative groups and some pharmaceutical studies because, in these cases, specimens are collected on behalf of the research sponsor who will maintain the samples in their own biobank. Such arrangements are generally clear in the funding agreement and will not be discussed here.

When the investigator initiates research including a biobank, the investigator often considers the research products to be their own. This belief is based on the individual investigator having created the biobank from conception, including the securing of funding, collecting and maintaining the valuable specimens and data. In many cases, university or external funding has not fully supported the costs associated with the creation and maintenance of these small biobanks, furthering the investigator's perception of ownership. Similarly, collaborating groups have promoted research and facilitated specimen collection. The intense interest of collaborating advocacy groups in the area under study often creates a tension with investigators as to the direction of future research on sometimes limited biobank resources.

Specimen donors, meanwhile, consider the specimens as parts of their persons and thus feel they have claim to certain rights and authority over how these pieces of themselves are ultimately used. Rather than thinking of the process as a "donation," to many participants it is a matter of entrusting their tissues/fluids and other biospecimens to the research team.⁶⁷ Specimen donors may not agree with subsequent areas of research and consider it a violation of their autonomy when secondary research proposes to involve their specimen(s).

The interests of all parties can be accommodated when all goes well, for example, when there is no significant financial value to the biobank, reliable funding is available and none of the research team decides to relocate the research and related biobank. Difficulties arise, though, in a number of situations. When funding to support ongoing maintenance of the biobank is lost, investigators often look to the university for financial support to maintain this research resource, which may not be forthcoming due to budget constraints. Additionally, should the research involving biobank specimens identify a commercially viable result, all involved hope to be included in any proceeds arising from the specimens. Lastly, investigators leaving the University may want to relocate the biobank to their new institution to continue their research. If the biobank is used by several investigators, some of whom are not leaving, the university is likely to want to maintain at least a portion of the biobank as an institutional research resource.

While there is a lack of clear consensus on how to balance the various parties' interests, some best practices are emerging. Consent forms must be clear as to what rights specimen donors will have in the future use of their specimens and whether they would receive compensation or other benefits from any intellectual property emerging from the secondary use research. Written agreements should be executed with collaborating groups which clearly define the roles of both the investigator and collaborating group in current and future research. Universities need to clarify policies and practices related to support

⁶⁷ Lynn G. Dressler, *Biospecimen "Ownership": Counterpoint*, 16 *CANCER EPIDEMIOLOGY BIOMARKERS & PREVENTION* 190, 190 (2007).

for and willingness to transfer biobanking resources. While the specific statements may not be agreeable to all parties, those who choose to be involved will at a minimum have a more complete understanding of what to expect in the future.

VI. MAINTENANCE OF THE BANK

The maintenance of a small-scale biobank is typically the responsibility of the investigator who established the bank. If the bank is established in conjunction with a particular funded project then the funds from that project are used to maintain the bank.

The literature contains general references to the importance of assuring quality control in different types of repositories,⁶⁸ as well as specific recommendations of how such quality control can be carried out.⁶⁹ These discussions, however, are typically linked to the issues in large-scale repositories, where automatization is essential. For small-scale repositories, quality assurance is, of course, a serious issue, but many recommendations available in the literature are not applicable, primarily due to the associated costs of building adequate infrastructures.

Yet, there are certain elements of the literature discussion that are applicable to small biobanks. These issues are (1) dupli/multiplicating each sample and assuring the presence of each sample in multiple locations in case of equipment failure; (2) establishing a transparent and clear way of sample labeling and monitoring (e.g., stock vs. working copes/aliquots); (3) preventing contamination; (4) automatizing, as much as possible, sample tracking and labeling; (5) guaranteeing the confidentiality and security of the stored specimens; and (6) assuring stable and adequate storage conditions.

For all these issues, there are two critical questions: how do investigators learn about the current best practices of biobanking? And who pays for both the acquisition of this knowledge and the establishment of the infrastructure that is necessary for the biobank maintenance? The literature, unfortunately, does not provide much guidance in addressing either of these questions. Much of the relevant knowledge has been accumulated through trial-and-error approaches while biobanking. It is important for academic and commercial banks to encourage their investigators experienced with biobanking to explicate and to share their technical knowledge, and to invest in infrastructure building and expertise sharing. Establishing and maintaining a biobank, even on a small scale, is a rather complex task that is both technically demanding and ethically charged. Single investigators establishing a bank should be exposed to both the relevant technical knowledge and the network of researchers and clinicians who have experience with biobanking.

VII. DESTRUCTION OF THE BANK

Little thought is often given to the closure of a biobank. For small biobanks, however, investigators move on to other projects and eventually the biobank specimens

⁶⁸ European Society of Human Genetics' PPPC, *Data Storage and DNA Banking for Biomedical Research: Technical, Social and Ethical Issues*, 11 EUR. J. HUM. GENETICS 906, 907 (2003); Jean-Marie Tiercy et al., *Quality Control of a National Bone Marrow Donor Registry: Results of a Pilot Study and Proposal for a Standardized Approach*, 32 BONE MARROW TRANSPLANTATION 623, 626 (2003).

⁶⁹ Thornton et al., *supra* note 40, at 1372.

are determined to be of no further value to the investigator. In some cases, there may be colleagues from other institutions interested in taking over the samples. Moving samples in this way will require appropriate clearances within the University, most likely including a material transfer agreement with the new “owner,” as well as ensuring appropriate shipping arrangements in accordance with the US Department of Transportation regulations.⁷⁰

In other cases, there is no interest in moving the biobank and, thus, destruction is warranted. A major factor in deciding to destroy a biobank is often that the funding is no longer available to support the continued maintenance of the specimens. The types of samples will dictate the necessary procedures, ranging from incineration of tissue samples to shredding of paper records. Destruction requirements for human biological specimens are generally covered under state law and hence vary from state to state. Investigators are advised to contact their institutional safety office regarding proper destruction. In addition to destroying the specimens themselves, some specimens may require that laboratory equipment used to process the specimens be decontaminated as well. Again the institutional safety office can advise on the specific case. Appropriate destruction of samples and decommissioning of the bank can have significant costs which are generally expected to be borne by the investigator at a time when reducing expenditures is the goal of the destruction itself. Universities and other research institutions should consider providing financial assistance for the dismantling of biobanks, as it will certainly encourage compliance with biohazardous waste requirements and prevent cheaper, improper procedures from being used.

VIII. CONCLUSION

We have reviewed a number of issues pertaining to biobanking on a small scale. Concluding this brief discussion, we offer a number of general conclusions. First, it is apparent that universities, whose mission is to advance knowledge, should consider supporting small scale biobanks as part of that mission. In particular, as the prevalence and promise of research involving biological specimens increase, universities should consider improving the infrastructure, including financial support, for the full life cycle of biobanks of all sizes. For example, there should be more educational/informational opportunities for single investigators to learn about legal, ethical, and practical aspects of biobanking. It also might be very useful for universities to offer small biobanks support from their central facilities (e.g., cryofreezing facilities) to minimize the possibility of accidental losses of various banked specimens. Second, the U.S. legislature should align the various regulations to facilitate a meaningful informed consent/authorization process for research participants considering specimen donation. Third, investigators should consider the full breadth of interested parties when developing banking projects, including the interests of patient and advocacy groups in addition to fundamental research questions. Finally, there should be ways for individual investigators who are interested in establishing biobanks to receive both ethical and technical training in the issues relevant to biobanking.

⁷⁰ See, 49 C.F.R. §171-178 (West 2009).