Banking on Trust

The Future of Research with Human Biological Materials
Why FasterCures Cares About Biobanking

FasterCures is not just our name, it’s our mission. We are an “action tank” that works to improve the medical research system—so that we can speed up the time it takes to get important new medicines from discovery to patients.

In fighting disease, patience is not a virtue. Patients are. We cannot conquer disease without engaging patients. The FasterCures Patients Helping Doctors (PHD) program focuses on building a culture of participation in research where patients and healthy volunteers understand the fundamental value they bring to clinical research.

We focus our efforts on unlocking patient information—medical records, biological material such as tissue, blood, and DNA, and our biology as observed in clinical trials—and making these available to clinical researchers in a meaningful way, including the willingness to donate human biological materials and clinical data to scientists.

By promoting ways to accelerate the collection and application of biological materials in research—biobanking—we can significantly advance the search for new diagnostic and therapeutic tools that are vastly lacking for scores of patients with limited or no treatment options.

We found that the key to achieving success in biobanking lies in building the foundations of trust among patients, advocacy groups, healthcare providers, and researchers.

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IN MARCH 2009, TIME magazine listed biobanks as one of the “Ten Ideas That Are Changing the World Right Now.” In an effort to assess current issues in biobanking, FasterCures conducted a series of interviews with experts in the field and surveyed the literature to better understand what is known about public attitudes regarding research use of their biological materials.

This analysis found that although there is great potential for improved human health in mining large collections of human biological material for research, TIME’s claims are a bit premature. Biobanks are changing how institutions conduct research, but they are not yet changing the world. Technical, institutional, ethical, and regulatory challenges remain, for example: 1) the quality of materials; 2) privacy concerns; 3) regulatory confusion; and 4) ownership, trust, and stewardship issues.

In many ways, the growing demand for access to human biological materials, combined with enhanced technological approaches to characterizing and studying those materials, do not raise any new issues, per se, in the world of biobanking. But many believe that the entire enterprise of biobanking has become more complicated and bureaucratic than it needs to be at a time when research tools increasingly offer improved ways to explore samples to better understand human disease.

This paper is based on an extensive literature review and key informant interviews with individuals familiar with the issues from several different perspectives. It briefly summarizes some of the barriers that remain and are growing in the world of biobanking, provides some examples of creative responses to meeting those challenges, and offers a simple, and perhaps overly simplistic approach, to moving forward. We found that the key to achieving success in biobanking lies in building the foundations of trust among patients, advocacy groups, healthcare providers, and researchers. Those who are collecting and using samples for research must earn the trust of those who donate their samples. There are a number of ways to earn that trust, as described in this paper.
A BIOBANK, ALSO KNOWN AS A BIOREPOSITORY, is a place that collects, stores, processes, and distributes biological materials and varying levels of data associated with those materials. Typically, those “biological materials” are human biospecimens—such as DNA, tissue, or blood—and the “data” might be as simple as the age and sex of the donor or as complex as comprehensive medical information about the person from which the sample came. A biobank can also include tissues from other animals, cell and bacterial cultures, and even environmental samples.

Modern comprehensive biobank facilities include all the necessary staff and management, ethical and legal oversight, financial systems, storage facilities, laboratories, security systems, and computer information systems to fully implement their operations. Commonly, a biobank also includes extensive modern molecular biology capabilities—such as robotics and automated micro-quantity liquid handling—to isolate and manage the chemical components (such as DNA) from those tissues. Today, biobanks exist inside a variety of settings, such as academic medical institutions, and pharmaceutical and biotechnology companies. They can also be stand-alone organizations, including independent companies (both for-profit and nonprofit) that can provide biobanking as an outsourced service or can serve as a broker of biological materials to other researchers. Several national governments have developed biobanking resources, as have some U.S. states.

The availability of high-quality biospecimens allows a researcher to conduct a wide range of analyses that permit a better understanding of the genetic and molecular changes involved in the progression of diseases, and can be used to assess the effectiveness of novel drugs and therapeutics in a particular patient population.

Nearly a billion stored specimens worldwide are likely to exist, based on extrapolations of estimates developed by the RAND Corporation. Thus, materials already gathered for a wide variety of reasons can be used in future research (retrospective collections) as well as ongoing efforts to prospectively collect and bank specimens based on specific scientific criteria or needs.

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Healthy volunteers also can donate blood or other material for research purposes. Increasingly, it is useful for the material to be stored with identifiers to enable researchers to retrieve relevant health-related information about the person over time. To protect patients and ensure privacy, samples may be coded, so scientists can obtain that information without ever knowing the identity of the individual. In some cases, identifying information is completely stripped from the material.

**The Increasing Value of Human Biological Material**

Pathologist David Korn, Harvard’s vice president for research and former dean of Stanford’s Medical School, has tracked the numerous scientific and medical advances that can be tied to the availability of vast amounts of human blood, tissue, tumors, and DNA. In 2000, he chronicled major advances up to that time, including discovery of the association between diethylstilbestrol (DES) and rare genitourinary cancers in daughters whose mothers were prescribed DES to help with certain complications of pregnancy. He described other linkages between environmental agents and some cancers, the causes of atherosclerosis, the discovery of oncogenes, and the genetics of colon cancer, to name a few. Human biological materials have been uniquely valuable research materials, routinely so for the past 150 years.

If processed according to the best standards, these specimens can last a very long time. For example, the National Heart, Lung, and Blood Institute has operated a repository since 1975, which contains 4.5 million samples of serum, plasma, whole blood, and white blood cells. Some of the samples have been frozen for 35 years.

In the past decade, new technologies—such as deep genome sequencing, high-throughput screening, and sophisticated assays—have made biological specimens even more informative; thus, there is growing demand for large collections of human biological material. For example, numerous genome-wide association studies (GWAS) are underway to identify common genetic factors that influence health and disease. GWAS encompass studies of genetic variation across the entire human genome, designed to identify genetic associations with observable traits (or phenotypes, such as blood pressure, height, disease state). The study of whole genome information in combination with clinical and other phenotypic data offers the potential to understand the basic biology and
etiology of disease. However many thousands of samples are needed for these studies.

In addition, a growing focus on “personalized medicine” requires that science delineate genetic variations among populations responsible for disease susceptibility and response to therapy. To understand the contribution of variants to the development of most common diseases, large numbers of samples must be studied. Information gleaned from these biological materials can be stored in large datasets, which can then be combined for ongoing analyses.4

The Growing Complexity of Biobanking

There is increasing demand for access to large collections of human biological materials such as blood, tissue, tumors, and DNA. Sometimes, technical and scientific needs dictate that material be collected prospectively for current and future studies. Other times, existing collections, of which there are thousands, can provide material of sufficient quantity and quality to explore some fundamental research questions. To adequately study a disease, investigators need tissues with that disease as well as healthy tissue and matched, non-disease tissue to use as controls. Growing demand for specimens has transformed what used to be an institutional activity typically involving a pathology department and a handful of researchers into a complex infrastructure. Watson et al., describe the current state of biobanking.5

Biobanking has expanded to embrace a range of specialized components including frameworks (ethics, privacy, security), equipment (processing, annotation, storage), operating procedures (biospecimen accrual, processing, annotation, storage, release, distribution, tracking), clinical informatics (pathology, treatment, and outcome data), database structures (donor consent and preference lists, inventory management tools, query tools), policies (priorities and access processes), economic models (funding sources, user fees, intellectual property), governance models (for strategy and operations), and personnel with specialized roles and training.

An entire “industry” has developed around biobanking issues. For example, professional associations have formed around the field, entire conferences are devoted to technical, ethical, and regulatory issues, and courses and training programs are offered to members of the Institutional Review Boards (IRBs) responsible for reviewing human subjects research using biological materials.

Some biomedical researchers have been concerned for some time about the growing debates about research use of human specimens and the burgeoning bureaucracy formed to review, manage, and regulate such research.

In a 2005 article in the Journal of the American Medical Association, Korn and Hakiminian wrote:6

Historically, research on human tissue samples has been relatively unencumbered by federal regulations and occurred without delineation of ownership rights to the specimens, patient data, or research products. As regulations have become increasingly restrictive, and because clear ownership interests have never been established, the presumed right of researchers and institutions to collect, use, and dispose of specimens and their associated patient data has remained undefined and occasionally contentious.
OUR INTERVIEWS AND LITERATURE REVIEW did not uncover any novel issues in the field of biobanking. Rather, we found that scientific, ethical, legal, and regulatory trends have magnified persistent infrastructure and oversight challenges to conducting research with banked biological specimens. These focus on:

- Standards, informatics, and interoperability
- Quality and utility of specimens
- Ethical and legal issues concerning privacy and consent
- Regulatory concerns
- Use and control of materials in research, including sharing among investigators

Improving the Science of Science with Specimens

Not all biological samples are created equal, and that can be a serious barrier for scientists. Processing and storage of samples varies, as do the methods for characterizing the material itself, resulting in uneven quality. In addition, the informed consent provided for different collections vary as well as the documentation of consent (e.g., paper, digital, microfilm).

The methods for collecting, storing, describing, and documenting information about specimens vary across and within organizations. Large sample sets should be collected in a consistent manner, correctly catalogued, and annotated in a standard or interoperable format. Pooling can enhance the power of a study. However, if samples are to be drawn from banks at multiple institutions there has to be some common system and language for describing them. Lack of standardization is inconvenient and costly, but more importantly, can lead to erroneous research conclusions.

In 2008, the National Cancer Institute (NCI) surveyed 727 cancer researchers about availability of biospecimens for research: 70 percent said they could not always access the number of specimens needed for their research; 80 percent said those that were available were of substandard quality; 60 percent questioned their results because of the quality of the material; and 80 percent reported limiting the types of research pursued because of a lack of sufficient high-quality specimens.

NCI’s Carolyn Compton has been tasked with some of the technical challenges facing the biobanking infrastructure. The NCI Office of Biorepositories and Biospecimen Research (OBBR), which Compton heads, was established...
in 2005 in recognition of the critical role that biospecimens play in research. The office is responsible for developing a common biorepository infrastructure that promotes resource sharing and team science, in order to facilitate multi-institutional, high-throughput genomic and proteomic studies. Compton also directs an effort in cancer called the Cancer Human Biobank, or caHUB, which aims to modernize the field of biobanking and contribute to medical advances by providing high-quality human biospecimens and data as well as analysis, scientific tools, and services to the cancer research and product development communities.

OBBR has established guidelines and standards for specimen collection and research use. The office has been leading the way at NIH, and some of the individual NIH institutes have established their own efforts. For example, the NIH Office of Rare Diseases Research is focused on efforts to coordinate banking of materials for rare disease research, which often suffers from lack of sufficient biological material at individual institutions. Such central biobanks, which are springing up all over NIH and in numerous large medical centers, are aiming to make reliable high-quality specimens easier to acquire and use, particularly in studies requiring thousands of specimens. NCI has also been involved in a trans-NIH effort to develop a policy framework on legal and ethical issues that would apply to all NIH-supported human specimen collections.

Compton credits Helen Moore, a molecular biologist who leads NCI’s Biospecimens Research Network, with identifying the need to fund studies in which the biospecimen is the subject of the research. This is critically needed because most technical procedures used by biobanks are based on empirical procedures that have come from collective experience rather than purely objective data. This has stymied efforts to produce specimens that are fit for research. Moore and others are trying to develop technology and standards for procurement, stabilization, and all of the steps in the process of using samples for research. Quality control varies among banks, which makes pooling samples for research problematic.

One creative solution to standardization and improved access is developing in the Southwest. In 2009, the Arizona Biomedical Research Commission announced a partnership with 5AM Solutions to create a virtual tissue bank—essentially a Web-based biological specimen tracking software system (using caTissue Suite, an open-source product from NCI’s caBIG program). Tissue data are structured in a standardized format that allows researchers to browse and search the database for samples suitable for their research needs. Consolidation of tissue data from multiple institutions will provide researchers with access to a very large collection of samples. The actual samples remain in the repositories of the participating institutions until needed by researchers, which minimizes transport and handling of the samples and possible degradation of quality.

However, the nature of the research defines the parameters for acceptable sample quality. Some investigators and repository managers argue that not all research requires gold standard material; that is, some good and valid work can be done on samples that are less than perfect, as long as the limits of the material are recognized. Thus, enforcing one-size-fits-all for repositories may ultimately raise costs and force some banks out of business. Others worry about the effects of such standardization efforts on existing banks, some of which have been operating for decades.
In addition, Compton says that we don’t have a good handle on the economics of biobanking—that is, we don’t understand current costs, including labor and infrastructure, or of redundancy of efforts, or lack of quality control. Despite the incredible research value of this material, she says we don’t sufficiently fund those professionals who make it their job to do this right—that is properly and ethically obtain, label, characterize, and store materials. In addition, the time and resources incurred by clinical personnel in obtaining consent, collecting specimens, and ensuring that they end up in the right hands are not reimbursable.

Protecting Donor Privacy
The information contained in a single human cell is so vast it is difficult to appreciate, given its size. The entire complement of DNA is contained within, as are the secrets of how cells grow, differentiate into tissues and organs, communicate with each other, become diseased, and die.

Although scientists have long studied human cells to understand, diagnose, and treat disease, technological breakthroughs and powerful new molecular techniques allow cellular information to be mined in ways never before possible. Thus, human biological material—whether cells, tissues, organs, or subcellular structures such as DNA—have become one of the most valuable research resources available to science. At the same time, their use raises ethical issues deserving careful consideration because such material also contains information that is unique to the individual from whom it came—for example, the existence of tiny mutations that affect health and predict future disease.

Most of the debate about biobanks has centered on whether donors could be harmed in some way by the information contained in the material or by a database getting into the hands of someone who does not have the best interests of the donor in mind or who does not know how to interpret the information.

For example, an employer paying for an employee’s health plan may receive information about an employee’s health status, resulting in loss of employment or loss of healthcare coverage. Or, an individual may receive information about the results of research with his or her biological material that leads him or her to pursue inappropriate therapies. Thus, whether the donor can be traced from the material or the data is central to privacy concerns.
A variety of approaches have been used to address this issue, ranging from completely de-identifying material and information so there is no way for anyone to know whose information it is, to designing an informed consent process in which donors understand and accept any risks associated with the research, including the potential for identification.

**Regulatory Concerns**

The ability to identify donors is also central to how biomedical research in general, and research with human biological materials specifically, is regulated by the federal government. The regulatory framework for research involving human subjects can be confusing because one must first determine whether the activity meets the regulatory definition of “research” and then determine whether the individuals whose materials and information are being obtained meet the regulatory definition of “human subjects.” Additionally, two sets of regulations exist—one for most federally funded research (45 CFR 46, or the Common Rule) and one for research subject to Food and Drug Administration (FDA) review and approval (21 CFR 50 and 56). Both sets of regulations use the term “human subject” but not in the same way.

Trying to determine whether research with biobanked material is subject to regulatory oversight rests on determining whether human subjects are involved. Determining whether human subjects are involved rests on identifiability. FDA, federal funding agencies, and even the Health Insurance Portability and Accountability Act regulations vary on what constitutes identifiability, creating a Byzantine maze for biobanks and their users. The reason this matters is that once research with biobanked material is determined to be human subjects research, ethics review and approval is required by an IRB, and informed consent must be obtained from donors, unless the consent requirement is waived by the IRB. These dual requirements—review and informed consent—can be substantial, in terms of time and resources, and in the view of some, burdensome, given the level of risk involved.

Stakeholders have repeatedly called for harmonization of the regulatory language in general, and more specifically with regard to the status of human biological materials, but little progress has been made. For example, in 2007 the Public Responsibility in Medicine and Research (PRIMR) Human Tissue/Specimen Banking Working Group published a paper addressing some of the legal, ethical, and policy challenges related to collecting, storing, distributing, and using human specimens and associated data for research. The group suggested strategies for the Department of Health and Human Services (HHS), FDA, and others to harmonize and clarify regulatory and consent requirements for research with biological specimens and to assist IRBs in assessing levels of risk. According to Pearl O’Rourke, director of human research affairs at Partners HealthCare Systems and one of the authors of the paper, little progress has been made in an area in which clearer federal guidance is sorely needed.
The HHS Secretary’s Advisory Committee on Human Research Protections, which provides advice to the Office for Human Research Protections, has created a Subcommittee on Harmonization, to “identify and prioritize areas in which regulations and/or guidelines for human subjects research adopted by various agencies or offices within HHS would benefit from harmonization, consistency, clarity, simplification and/or coordination.” It is not clear when this group’s work will be done, and once done, whether the relevant agencies will heed its advice.

Making Biobank Materials Anonymous

According to federal regulations for the protection of research subjects, if an investigator can identify or readily ascertain—either directly or indirectly through coding systems—the identity of the living individuals from whom the specimens came, then the research involves human subjects. And, as with any other type of research involving human subjects, protections must be in place to safeguard the best interests of those who consent to the research use of their material. One measure is to ensure that the materials are stored in a secure way so as to protect the confidentiality of those who have donated samples.

Because the extent to which biological material can be linked to the person from whom it was obtained can affect risks to subjects, some biobanks have opted to mitigate risk by removing all identifiers. Although this solves one problem, it can create another. In a majority of cases, specimens are more valuable to researchers if relevant clinical information about the source is known. For this reason, many biobanks have some mechanism for keeping a record of individual identities—most often through a third party or a secure coding or encryption system. This allows the biobank to obtain relevant additional or clinical information, if the original informed consent agreement allows for such data gathering.

However, technology is finding ways around even the most sophisticated encryption systems—(although no evidence exists that anyone has tried to crack such codes or compromise existing datasets). A 2008 paper by Homer et al., described a statistical method for resolving individual genotypes with a mix of DNA samples or data sets containing aggregated genomic data, for example, as found in large genomic databases.10 The authors concluded that “These findings also suggest that composite statistics across cohorts, such as allele frequency or genotype counts, do not mask identity within genome-wide association studies.”

This potential capability changes the risk calculations for breeches of privacy. In general, encryption and coding schemes have been presumed to protect subjects’ confidentiality and privacy. It is not clear whether such measures can continue to ensure protections in light of this new development. In theory, any individual whose genomic data are in a database can be identified if an identifiable comparison sample from that individual is available. With enough data available, one could determine whether an individual participated in a study although one has to question why anyone would pursue such a needle in a haystack, given the time, expense, and unclear benefit. However, the mere potential for such a breech has had important policy implications for how the scientific community shares pooled sets of genetic data and spurred the development of an entirely new oversight system being constructed to guard against such a risk.
Consent Issues

Few would argue that scientists should be able to obtain identifiable specimens from individuals and use them for research without their knowledge. And, in most cases, consent is required for such use. What remains contested is how much individuals need to be told, when they need to be told, and what they can be allowed to decide for themselves about how materials will be used in research.

Add to this the complications that arise from researchers wanting to use materials that already sit in storage, some for decades. Materials and clinical data might have been collected under terms that do not meet current standards (although they were acceptable at the time of collection). Or, donors might have consented to one type of research—for example, diabetes—but were not asked about others that were not even contemplated at the time—for example, genetics of heart disease (so-called “secondary uses”). Because of these circumstances, some IRBs have not approved the creation of aggregated biobanks or databases or have limited the types of studies that can be done with them, even when additional studies are considered appropriate under the terms of the original consent. Their concern is that if the donor did not provide explicit consent to all planned uses of the material, then the material cannot be used unless the donor is located and asked to provide consent for the new research study. Although this approach provides an extreme level of protection, it is not always feasible, practical, or affordable. Some have suggested the use of “consent waivers” whereby an independent third party determines whether subsequent research using biobank materials is consistent with the original consent provided. In fact, this is what IRBs do on a regular basis, a process that is time consuming and costly.

Another view is that “blanket consent” to all future research should be sufficient; that people are wise enough to understand that their tissue might be useful in future studies, and are capable of consenting to all such potential uses, with the assurance that information obtained through the research will remain confidential. Numerous studies have shown that a sizable fraction of the general public are comfortable with unlimited future research on their biobanked materials, without the need for re-contact and re-consent for every use. However, there are cultural and contextual differences. For example, individuals in countries with national health services tend to be less concerned about harms that might occur from future uses of specimens than are groups in the United States.

What remains contested is how much individuals need to be told, when they need to be told, and what they can be allowed to decide for themselves about how materials will be used in research.
Still, studies show an increasing willingness on the part of many Americans to provide blanket consent. However, research to understand these views are varied in methods and approaches; for example, some surveys have only asked whether people would worry about risks versus whether they would actually refuse to donate and provide consent. To illustrate, even though one study found that 90 percent of respondents would be “concerned” about risks to privacy, 60 percent would actually participate in a biobank, and nearly half would provide blanket consent.

For the minority who are not comfortable with providing such blanket consent, they should withhold it and should not donate their specimens if they feel conditions are uncertain.

Those who believe that people are capable of understanding and providing blanket consent also believe that it is impracticable and even intrusive to track people down years after a biopsy to ask if their stored tissue can now be used in a new study. Such actions offer little if any additional protection in an area of research where risks tend to be minimal. In addition, the only way to avoid such a requirement is to seek a waiver of the informed consent requirement by an IRB, an option available under HHS but not FDA regulations.

Focus groups conducted in the late 1990s by the now defunct National Bioethics Advisory Commission and more recent surveys demonstrate that most Americans are willing to donate material to future unspecified research as long as they are asked in advance and are comfortable that research results will not be shared with third parties who might not have their best interests at heart, for example, employers or insurers.

In sum, if concerns about breaches of privacy or confidentiality are the primary deterrent to streamlining and simplifying the consent process for biobanking, it seems that science and the public health would be far better served by removing the potential for such harms occurring. Sophisticated encryption systems and public policies that outlaw medical discrimination seem preferable to slowing or restricting critical research efforts through unnecessarily restrictive interpretations of what constitutes informed consent. Holding institutions and biobanks liable for privacy breeches is another way of mitigating risks.

**Ownership and Control of Specimens**

The issue of consent is sometimes entangled with issues of ownership and control of use.

Ever since the 1990 landmark case, Moore v. Regents of the University of California, in which the Supreme Court of California ruled that a patient (John Moore) had no property rights to his own leukemia cell line banked for research, there have been disputes about who owns, or should have access to, materials stored in biobanks. Until recently, courts have denied claims of ownership to one’s biological samples based on common law property or gift theories.

In Washington University v. Catalona, the Federal District Court for the Eastern District of Missouri held that individuals do not retain any rights to control their specimens once they have been donated. The Washington University v. Catalona decision clarified that donors do not have the right to revoke and physically repossess
donated specimens or to direct or authorize use or transfer of the material once it is donated. In this case, the donors did not want the tissues for themselves, they wanted to keep them in the hands of the researcher with whom they originally entrusted them. William Catalona is the urologist who developed the widely used prostate-specific antigen test for prostate cancer. He began collecting samples for research in the early 1980s and when he decided to move to Northwestern University School of Medicine, he tried to take his collection with him. It is important to note, however, that the federal regulations governing human subjects research do not permit the use of exculpatory language in consent forms, for example, “I voluntarily and freely donate any and all blood, urine, and tissue samples to [name of research institution or researcher] and hereby relinquish all right, title, and interest to said items.”

Six thousand of Catalona’s patients petitioned the university to release the samples, claiming that they had donated the samples to him—not to the University. But Washington University refused, claiming that the collection had been maintained with university funds and, moreover, it had become a broader resource that Catalona could not exclusively claim rights to.

However, the court also left open the possibility that individuals might have a continuing interest in their biospecimens. In a subsequent decision, the U.S. Court of Appeals for the Eighth District indicated that specimen donors can retain the right to discontinue further involvement in research by either 1) not answering any additional questions, 2) not donating additional tissue, or 3) disallowing the use of their tissue in future research.

Thus, court decisions have reinforced the notion that specimen donors have the right to discontinue future use of their specimens or data (assuming they can be identified for removal). However, the conditions and elements of a particular informed consent process could alter that interpretation. This was demonstrated in a recent settlement with the Havasupai Indians.

Members of the tribe had given DNA samples to Arizona State University researchers starting in 1990 for research on the genetic contribution to the tribe’s high rate of diabetes. According to an article in Science, 100 tribe members gave blood from 1990 to 1994 after signing a broad consent form that said the research was to “study the causes of behavioral/medical disorders.” The lead investigator said the consent form was “purposely simple” because English was a second language for many members of the tribe and few had graduated from high school. Investigators were
instructed to allow for questions and to obtain verbal as well as written consent.

When the tribe learned that the DNA was being used to study topics unrelated to diabetes, such as mental illness and the tribe’s geographical origins (which did not comport with their traditional stories), the tribe banished the investigators from their land and asked for return of the samples. The Arizona State University Board of Regents agreed to pay $700,000 to the tribe’s members, return the specimens, and provide other assistance to the impoverished tribe. The case highlights, among other things, the care that must be taken when working with vulnerable populations.22

More broadly, this settlement implies that the rights of specimen donors can be violated when they are not fully informed about the research uses of their specimens. As noted previously, often such uses cannot be anticipated, especially as increased understanding of the underlying bases of diseases reveals surprising associations, for example, between schizophrenia and autism, or between Down syndrome and Alzheimer’s disease. The Havasupai settlement is a reminder that some populations are not interested in providing broad consent, and the consent process and subsequent use of materials have to be clear and understood by all involved.

In addition to the need to clarify patient control over samples, institutions need to clarify and coordinate policies regarding how specimens will be shared internally and also with external investigators. Research in rare diseases and in

For the minority who are not comfortable with providing such blanket consent, they should withhold it and should not donate their specimens if they feel conditions are uncertain.
IN DEVELOPING THIS WHITE PAPER, several models for biobanking emerged that have managed to address some of the challenges described above, particularly with regard to recruitment and consent, review, ownership, and control.

**GENETIC ALLIANCE BIOBANK: A Patient-Driven Approach to Ownership and Trust**

One model that reinforces the value of trust in biobanking is the “patient-driven” bank, in which some rights are transferred to the community and access and use is controlled by the patients.23 In the United States, the Genetic Alliance BioBank is a centralized, advocacy-owned, biological sample repository. The BioBank provides shared infrastructure and tools for disease-specific organizations to build their own biobank and database. The cooperative effort currently has seven member organizations. Data mining software facilitates research use of the material and data. The Genetic Alliance BioBank sets standards for participant involvement in research, provides standardized protocols, allows for ethical re-contact, and provides robust protections in the context of the communities served by the membership advocacy organizations.

The Genetic Alliance BioBank is modeled after PXE (pseudoxanthoma elasticum) International’s efforts in 1995 to create a rare disease organization that initiates and conducts research on pseudoxanthoma elasticum, with affected families actively participating in gene discovery and patenting, and development of a diagnostic.

**KAISER PERMANENTE'S RESEARCH PROGRAM ON GENES, ENVIRONMENT, AND HEALTH: Banking on Health Benefits Driven Approach to Ownership and Trust**

The Kaiser Permanente Medical Care Plan of Northern California is home of the Research Program on Genes, Environment, and Health (RPGEH). The program includes a biobank that will be able to draw material and clinical information from as many as 500,000 consenting health plan members. The biobank will be linked with comprehensive electronic medical records, and data on relevant behavioral and environmental factors. The goal is to sort out the relative influences of genes, environment, and behavior on the development of chronic disease such as cancer, diabetes, and hypertension. All biorepository data and DNA samples are de-identified and stored in secure locations with limited authorized access. Biorepository data are not entered into patients’ electronic health records.

The project is funded, in part, through a $8.6 million grant from the Robert Wood Johnson Foundation’s Pioneer Portfolio, and through a $25 million grant from the National Institutes of Health. Only Kaiser Permanente Northern California members are eligible to participate in the program. The biobank is open to researchers from accredited institutions. Researchers have sequenced the DNA of 100,000 Kaiser Permanente member volunteers thus far, toward their goal of 500,000.

What makes the RPGEH unique is its ability to directly benefit individual patients, as research findings could be used to tailor treatments and prescribe lifestyle changes for specific populations of patients, for example, those with rare forms of cancer or genetic conditions. Another unique aspect is the inclusion of environmental information collected from a broad array of populations.
Vanderbilt University School of Medicine’s BioVU collects DNA samples extracted from leftover blood remaining after routine clinical testing. The DNA is then linked to a de-identified version of data extracted from an electronic medical record system, in which all patient identifiers have been removed. Thus, no identifiable private information is attached to the records. As of May 2010, the bank had obtained 87,000 adults samples, and more than 2,000 pediatric samples. Before obtaining pediatric samples, BioVU personnel conducted more than 100 interviews with parents to assess concerns. Daniel Masys, professor and chair of biomedical informatics at Vanderbilt, says BioVU is receiving as many as 450 samples per week. The biobank hopes to build the collection to more than 250,000 samples across all age groups.

BioVU adeptly addresses two challenges to biobanking (consent and usefulness of data) with one solution—de-identify all materials and data yet design a research methodology that makes maximal use of the resources available. Even though it took four and a half years to get the system up and running, the BioVU approach provides one answer to the tangle created by processes required, and the systems of safeguards to protect identities. Vanderbilt continues to operate other biobanks in addition to BioVU, although their collaborators can be from other centers. Researchers must agree not to try to re-identify patients and to notify BioVU if they come across information that could potentially reveal the identity of a patient. Because BioVU does not share its materials and data with external institutions, it does not have to have an acceptable use policy, as required as a condition for federal funding. However, the program does have a stringent system to monitor use by its own investigators.

Masys notes that another advantage of the opt out approach is that it relies on an opt out system for consent, even though regulatory requirements would not even require such a system since the samples are de-identified and, therefore, technically no “human subjects” are involved. Because of its de-identifying procedures, according to Masys, BioVU is one of the few biobanks that qualifies as non-human subjects research as determined by the local IRB and the federal Office of Human Research Protections. This determination, however, remains controversial, as some claim that the bank is identifiable, albeit only through a very careful and well-protected encryption process.

Under the procurement policy, patients seeking care at the Vanderbilt hospitals are told that leftover or excess materials will be used for the DNA bank unless they indicate that they do not want to participate, that is, they opt out.25 Initially, BioVU organizers predicted a 5 percent opt out rate, and that has been the case so far. These numbers match those found in studies of other opt out systems, for example in The Netherlands.14a;b Although no direct benefits are promised to patients who don’t opt out (i.e., opt in) other than altruism, BioVU organizers have built in a system by which to send clinical alerts and reminders to providers when research findings might have significance for their patients whose samples were analyzed. Because of an elaborate firewall system, the BioVU investigators have no way of knowing who received these alerts.

Masys believes that trust in Vanderbilt’s medical institutions, not so much as in medical science, is responsible for the high participation rate.
THE UK BIOBANK:
A National Effort Backed by a National Healthcare System Minimizes Fear of Discrimination

The UK Biobank is a massive national effort, with nearly 500,000 participants between the ages of 40 and 69 registered as of July 2010. The UK Biobank is a registered charity in its own right, and is funded by the Wellcome Trust, (the UK’s largest independent medical research charity), the Medical Research Council, the Department of Health, the Scottish Executive, the Northwest Regional Development Agency, and the National Health Service. The effort also has the backing of many of the UK’s major medical research charities, including the British Heart Foundation and Cancer Research UK.

To gain public trust and encourage participation, the UK Biobank has undergone rigorous review and consultation at all levels, beginning with a preliminary feasibility phase in 2000 and 2001. This ultimately led to a pilot study, which took place between March and June 2006, recruiting 4,000 participants from South Manchester. Key findings from the pilot projects and public consultations allowed the project to refine and improve the recruitment process. It also led to the development of a public Ethics and Governance Framework to set ethical standards for the project. As part of its process, the biobank sought approval in England and Wales from the Patient Information Advisory Group—representatives of patient groups, healthcare professionals, and regulatory bodies—for gaining access to information that would allow the project to invite people to participate. The project’s success in part is due to the availability of national healthcare in the United Kingdom, which, in general, eliminates fears about loss of insurance and access to healthcare based on pre-existing or emerging medical conditions.

THE UNIVERSITY OF PITTSBURGH:
Using an Honest Broker to Protect Privacy and Build Trust

The University of Pittsburgh uses a novel, IRB-approved collaborative mechanism, called the Honest Broker Service, to meet the specimen and data needs of researchers requiring clinical information about the donor. The mission of the Honest Broker Service is to ensure regulatory compliance for the release of information involving clinical and research data stored in applications developed, managed, or used by the university healthcare system. There are 28 Honest Brokers included in this service, handling thousands of requests, including 12 brokers from the tissue bank. All Honest Brokers involved with this service are certified in accordance with university and IRB policy. Materials published by the University of Pittsburgh state that “The overall attempt is to obtain ‘informed consent’ from all patients for research use of their biologic materials. In addition, the various registries at the institution attempt to obtain ‘informed consent’ from all patients for the research use of their data”.

Essentially, the Honest Broker acts as a well-defined barrier between the clinical environment (in which fully identified confidential patient information is routinely exchanged as part of medical care) and the general research community (in which all information must be completely de-identified).

In its purest form, the Honest Broker is not part of either the clinical or research team and is the only person or organization that can link research identifiers and clinical identifiers. By using the Honest Brokers, control and responsibility of the de-identification process is placed in the hands of an independent third party, reducing the risk of conflict of interest. Personal and clinical identifiers are limited to the clinical space while research identifiers are never tied to personal or clinical identifiers except through the Broker’s code book. The system ensures that new clinical outcome information can be added to a file identified only by a code number, not a name. Additionally, in the rare event that important research data become available and it becomes necessary to inform the patient or their survivors, a fail-safe mechanism exists for such information to reach the interested party. A 2008 study of the program concluded that this approach has provided a highly functional solution to ensuring that researchers gain access to critical clinical information in a way that protects the interests of the research subject.
ONE OF THE CONCLUSIONS TO DRAW IS THAT TRUST—AT MANY LEVELS AND IN MANY FORMS—IS ESSENTIAL FOR THE SUCCESS OF BIOBANKING.

Russian writer Anton Chekhov once said “You must trust and believe in people or life becomes impossible.” Some have felt that a breakdown in trust, or the perception that trust should not be assumed, has made the current biobanking system nearly unworkable—that the growing systems of protections are onerous, expensive, and excessive when compared to the level and likelihood of risk. Others have found that creating trust is the best investment in their banking efforts:

• In the case of BioVU, much trust was invested by patients in the Vanderbilt healthcare system, which has been providing the community with quality healthcare for generations.

• The Genetic Alliance BioBank succeeds because the patient advocates control access and use, building a system of trust in the patient community.

• The UK Biobank succeeds because the program invested in an intensive community consultation effort to understand patient concerns and to educate potential registrants. This built trust in the effort, which has the advantage of being backed by a national health service that will not deny care or coverage to individuals based on research results.

• The University of Pittsburgh Honest Broker system succeeds by ensuring patients that their data will not be accessible to individuals not who do not share their best interests.

There are many other models; these are but a few. No one would suggest that biobanks and the scientists who use them should be free of oversight or that patients and healthy volunteers should not be informed that materials will be used in research. The examples provided above demonstrate that reasonable approaches can be taken to ensure that oversight is in place in such a manner that research can ethically proceed and that risks to individuals are minimized to the extent possible. There is always a risk of bad actors in any system but we need to question whether building policies around the exception, rather than the rule, is slowing healthcare advances.

In building and sustaining biobanking efforts, the research and patient communities might consider a few principles, not prescriptions, to help facilitate progress.

1. The public needs to understand that medical progress is dependent on wide participation in research. The benefits of donating biobank materials for research accrue to all individuals and future generations.

2. Most people authorize the unlimited future use of their biological materials when given that option in a clear and
We need to do better in crafting a consent (or opt out) mechanism that outlines a scope of research that is fairly broad. We have to remember that consent is a voluntary process. Reasonable policies should not focus on ensuring that everyone will provide consent. Rather we should be seeking a policy that allows potential donors to consider whether blanket consent is sufficient for their decision making purposes, and if so, to autonomously make the choice to bank their specimens for future research.

Oversight mechanisms should be commensurate with the level of risk involved. We need to pursue novel approaches, like some of those described here, to review biobank operations. For example, some biobanks might pursue one mechanism to review the collection of specimens, and another to review use—but only if that is more efficient and ethically sufficient.

To gain and ensure public trust, biobank governance and leadership must continue to engage in public consultation and education.

Biobanks and the research community must assert stewardship of this valuable resource by ensuring that the appropriate protections are in place and that everyone understands their responsibilities and obligations in the protection system.

Research with biobanked materials is dependent on quality controls and assurances. Although experts debate how high to set the quality bar for a given study, minimal standards are essential to protect the integrity of the sample, which is a gift, and to protect the integrity of the research results.

Finally, resources are needed to support the careful collection, storage, and maintenance of specimens. Clinical personnel who take the time to explain the importance of clinical research using biological materials, and ensure that patients and healthy volunteers understand the benefits and risks before consenting, should be able to be reimbursed for their time (for example, through the creation of a CPT code [Current Procedural Terminology] for clinical research activities).
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