The ethical use of existing samples for genome research

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Abstract: Modern biobanking efforts consist of prospective collections of tissues linked to clinical data for patients who have given informed consent for the research use of their specimens and data, including their DNA. In such efforts, patient autonomy and privacy are well respected because of the prospective nature of the informed consent process. However, one of the richest sources of tissue for research continues to be the millions of archived samples collected by pathology departments during normal clinical care or for research purposes without specific consent for future research or genetic analysis. Because specific consent was not obtained a priori, issues related to individual privacy and autonomy are much more complicated. A framework for accessing these existing samples and related clinical data for research is presented. Archival tissues may be accessed only when there is a reasonable likelihood of generating beneficial and scientifically valid information. To minimize risks, databases containing information related to the tissue and to clinical data should be coded, no personally identifying phenotypic information should be included, and access should be restricted to bona fide researchers for legitimate research purposes. These precautions, if implemented appropriately, should ensure that the research use of archival tissue and data are no more than minimal risk. A waiver of the requirement for informed consent would then be justified if reconsent is shown to be impracticable. A waiver of consent should not be granted, however, if there is a significant risk to privacy, if the proposed research use is inconsistent with the original consent (where there is one), or if the potential harm from a privacy breach is considerable. ***Genet Med* 2009:11(10):712–715.**

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Translational research, so-called "bench-to-bedside" investigation, is critical to our understanding of how fundamental scientific observations pertain to the human condition. Research using animals has comprised much of our efforts to understand how any factor may affect the in vivo situation. However, animal models do not always reflect what is clinically relevant in the human. Moreover, ethical considerations require researchers to justify the need for live animals ("replacement," if possible), to minimize stress to animals ("refinement" of experimental procedures), and to justify the numbers of animals required (reduction) to prove any scientific tenet.[1] Studies on human tissues fulfill these needs,[2] providing snapshots of the in vivo situation in humans, effectively reducing the need for animal experimentation.

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The scientific community's recognition of the relevance of human tissue research has prompted an explosion of biobanking efforts in which participants are consented a priori for access to their tissue as well as linked clinical information for the purpose of research. These efforts have further been spurred by the availability of new technologies to quantify biomolecules in a multiplexed fashion (e.g., cDNA microarrays, mass spectrometry, and nuclear magnetic resonance spectroscopy). These developments have dramatically accelerated the capacity to identify biomarkers for diagnosis, prognostication, and prediction of therapeutic response or disease susceptibility.

But biobanking with prospective consent is only a relatively recent movement, and biobanks do not frequently contain sufficient numbers of samples from rare diseases or specific populations. Archival tissues collected as a matter of normal clinical practice by pathology laboratories or for research purposes but without specific informed consent remain rich sources of biomolecules potentially available for research. Rare diseases and populations are better represented in archival collections. Moreover, because such samples have been collected over many years, long-term clinical outcomes such as survival are often known, making the tissues even more valuable for biomarker research. Conversely, patients have typically not consented to use these tissues for the proposed study (or for research at all) nor have they consented to access of associated clinical data. In the past, research efforts using archival tissues have typically occurred without the explicit knowledge and consent of the patients from whom the tissue was derived. More recently, those practices have been challenged. Patient advocates have been critical of the involuntary inclusion of tissues from unconsented patients in published or commercial research[3]; and there have been challenges from individuals whose tissue was the source of intellectual property.[4,5] When samples are used without explicit consent, participant autonomy is not respected, which particularly affects individuals whose cultural beliefs require access to all body parts for burial or individuals concerned about invasions of privacy. Further, even though US courts have ruled that individuals do not retain ownership of their excised tissue, participants may have a dignity-based objection to the use of their biological specimens in certain types of research. Indeed, public scandals related to the removal of tissues from unconsented donors, such as the Alder Hey incident in the United Kingdom, have resulted in the loss of credibility of investigators and forced the dissolution of large collections accumulated over many years.[6]

The generation of genetic information and recent policies that require broad data sharing[7] raise additional privacy concerns that further complicate the issue. However, few guidelines are currently available for access to existing biological samples, especially for use in genetic research.[8,9] It is our intent to define an ethical framework for accessing archival tissues, taking into account the needs of the research community, as well as the rights and expectations of participants. The ethical framework is most relevant to any human studies designed to identify genetic associations with observable traits, especially genome-wide association studies. However, the principles can be applied to nongenetic biomarker studies using archival tissues. The pro-

posed ethical framework does not target any particular country or region because ethics board oversight is a fundamental requirement, ensuring consideration of local cultural biases.

PRIVACY CONCERNS

The ideal data repository for research includes demographic and clinical data, pathology data, and information on the tissues banked, including genomic analysis, as well as the circumstances under which the biological specimens were collected. Linkage of all of these data elements enhances scientific utility. At the same time, the data represent a significant risk to the donor. If not sufficiently protected, such data could be used for discriminatory or stigmatizing purposes by third parties such as insurance companies, employers, and governments.

Anonymization (the removal of all personally identifying phenotypic information [e.g., name, address, social security number, and medical record number] within a database that could be used for backtracking to an actual patient) has been proposed as a solution to privacy concerns. This seems to be acceptable to the majority of the American lay public.[10] But anonymization represents a double-edged sword. On the one hand, it provides some privacy protection. On the other hand, anonymization may risk the scientific value of the biospecimens, as the data are more difficult to check and validate, and it is much more difficult to track longitudinal changes as the patient's condition changes. Importantly, anonymization may preclude any influence the donors have on the use of their samples. Furthermore, anonymization is becoming increasingly more difficult to achieve because biological information such as genomic information is generated, for that information itself is unique and identifying.[11–13] Thus, although anonymization appears at the outset to provide some benefit to protecting participants' privacy, it is an imperfect solution.

Although many ethicists have acknowledged the importance of genetic privacy, not all would agree that genetic privacy is a premise that requires special consideration.[14] Genetic exceptionalists would argue that because DNA is easily procured, stored, and accessed and because it contains information on the person's (and kin's) future risks of various diseases, it ought to be treated as special and afforded heightened protection.[15,16] Conversely, commercial enterprises as well as some academic researchers have an interest in making it relatively easy to access DNA samples that can be linked to medical records. They might argue against new rules governing genetic privacy on the basis that genetic information differs little from other sensitive medical information.

From a more pragmatic perspective, because it is difficult to limit access to genetic information, some (including Francis Collins and Craig Venter) have advocated genetic antidiscrimination laws instead of genetic privacy laws. These laws would protect against the misuse of genetic information to avoid potential harms (e.g., discrimination from governments based on the ethnicity or susceptibility to mental illness, discrimination in health coverage by insurance companies based on the disease susceptibility, or discrimination by employers because of behavioral predispositions). Indeed, in the United States, a federal antidiscrimination law specifically designed to protect people from discriminatory behavior based on the genetic information was recently enacted.[17] The Genetic Information Nondiscrimination Act generally prohibits health insurers or health plan administrators from requesting or requiring genetic information of an individual or the individual's family members. Genetic information cannot be used for decisions on health coverage, rates, or preexisting conditions. The law also prohibits most employers from using genetic information for decisions on hiring, firing, or promotions. Thus, at least in the United States, even if privacy cannot be completely assured as genetic information is generated, the donor is assured some protection from harm related to misuse of (identifying) genetic information.

Concerns about the identifiability of research participants and their individual privacy are also heightened in the context of other potentially sensitive or stigmatizing investigations (e.g., research on determinants of mental illness, drug addiction, intelligence, and criminal propensity,[18] as well as research on human immunodeficiency virus and obesity[19,20]). Similarly, research on small defined populations, particularly those with a propensity to certain disease states, are potentially stigmatizing.[21–23] Like genetic research, this research mandates special consideration not because of the known risks associated with it but because of the magnitude of the potential risks, such as adverse effects on employment, insurance, health care, or social interactions. Given this uncertainty and the potential consequences, a prudent approach would be to treat the risk as significant until proven otherwise.[24,25]

PROTECTION OF AUTONOMY

To fully respect autonomy, informed consent is required. To this extent, modern biobanking efforts are much better equipped for fulfilling this ethical obligation. Several studies have been conducted, which illustrate the lay public's desire to participate in the decision to provide tissue for research. In the report by Dawson,[26] lay public focus group members considered consent mandatory for any tissue procurement for research. Interestingly, consent was also viewed as a courtesy expected of the medical community, imbuing trust in donors. If genetic information is generated, then there may be wide variation in participants' comfort related to sharing those data, although in a recent focus group study, participants felt that explicit consent is required if there is public data sharing.[27]

In the case of accessing archival samples, consent is not easily obtained without considerable economic expense and practical obstacles and may, in some cases, be impracticable. It has been argued that recontacting patients/participants (or their families, if deceased or incapacitated) itself represents a privacy intrusion, particularly when requesting consent from the family of a deceased individual.[28] Additional distress may arise from concerns about how they have been identified by a researcher who is not directly involved with their clinical care. From a scientific perspective, obtaining consent for research on previously collected specimens may induce a selection bias because of dropouts, interfering with scientific validity.[28,29] Finally, it has been argued that the value of biomedical research benefits future patients and society as a whole, justifying use of archival tissues even in the absence of consent.[30]

There is therefore a reasonable argument for accessing archived tissues without consent at the expense of donors' autonomy. Indeed, there does seem to be some tolerance by the lay public for use of archival samples without consent. Pulley et al.[10] surveyed lay persons on whether they would accept the creation of a large-scale effort to collect genetic samples from excess clinical blood specimens. Almost 90% of respondents were comfortable with anonymized genetic information and 98.7% of respondents supported the potential benefits. Dutch patients who had undergone surgery for breast and colorectal cancer were surveyed for their preferences related to consent procedures.[31] Patients indicated that opt out consent (whereby patients are not actively asked to make a decision about research with their tissue but are given the option to opt out) would

suffice as long as they are adequately informed. In a study by Hull et al.,[32] most respondents thought it would be important to be informed that research would be performed with their sample, regardless of whether the samples were anonymous or identifiable. Of those who considered it important to be notified, 57% would require their permission to be sought before their samples would be used; the remainder would be satisfied by notification only. Thus, although many are tolerant of researchers accessing their tissues, it seems that a significant number desire at least some disclosure about how tissues are used.

It is acknowledged that the use of archival tissues without consent is suboptimal, because participants are not given the option to participate.[33] Conversely, to simply discard such a resource, which may provide a means for improving our understanding and medical management of human disease, may also be objectionable. In 1995, the Nuffield Council in the United Kingdom acknowledged that archival tissues in pathology tissue banks represented an important source of scientific knowledge.[34] Thus, in that country, use of such tissue has effectively been legitimized. Although such a focused examination of the issue has not been duplicated in most countries, the use of archival tissues for research continues to represent a common practice throughout the western world. Indeed, it remains permissible to use coded tissues for research in the absence of consent in Canada, Germany, Norway, the Netherlands, and United States.[35]

This practice, however, has been publicly challenged in the context of research that is potentially stigmatizing or that involves an identifiable cohort. For example, there was public outcry when samples that were collected from the Havasupai tribe for diabetes research were subsequently used for research on schizophrenia and inbreeding.[23,36] Because such research was potentially stigmatizing and because migration research could potentially conflict with the religious beliefs of the Havasupai, there is a strong argument that informed consent should have been obtained. In this case, the potential risks mandated respect for the autonomy of sample donors, regardless of the expense or other obstacles to reconsent.

The Havasupai case also illustrates the risks associated when stored samples collected for one purpose are used for a secondary purpose. Again, studies on donor preferences may be instructive. The majority (61%) of Scottish lay persons questioned about the use of stored blood for DNA biobanks were unequivocally supportive of storing blood for this purpose.[37] However, when asked about open-ended consent, respondents did express concern regarding future uses. A Swedish cohort was surveyed about whether it would be permissible to use stored blood for "future research on cardiovascular disorders and diabetes."[38] Of the 93% who provided consent, 22% wanted to be informed about and provide new consent for each new genetic project. Thus, even among those who are supportive of biobanking, there is a significant subgroup who is hesitant to provide a "blanket" consent.

A FRAMEWORK FOR ACCESSING ARCHIVAL TISSUES AND CLINICAL DATA FOR RESEARCH

The fact remains that archival tissues represent an important scientific resource, allowing research on the determinants of long-term clinical outcomes and susceptibility to disease. Discoveries derived from such tissues are more likely to have direct benefits to mankind than research using animal models. For these reasons, translational research based on such tissues should be encouraged. However, given the complexity and uncertainty of potential risks to participants, guidelines defining the conditions for accessing these tissues are important.

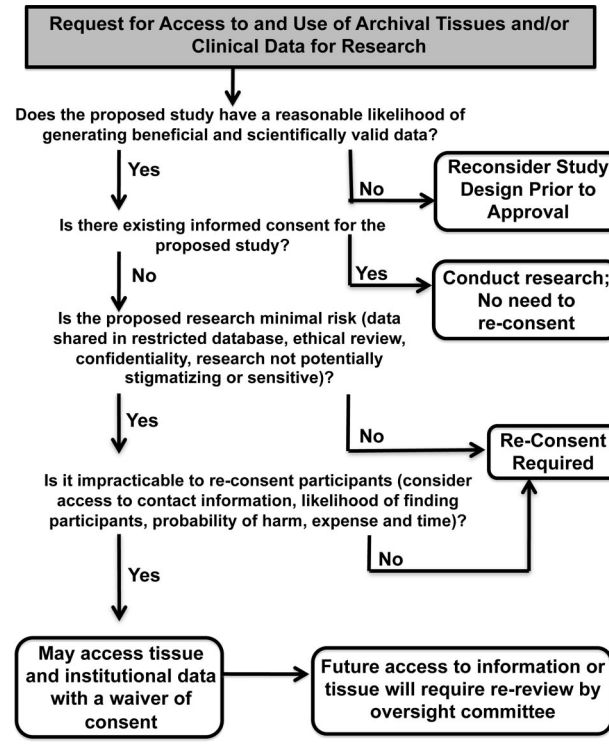

Fig. 1. A framework for accessing archival tissues and clinical data for research.

Helgesson et al.[29] have provided one ethical framework for using previously collected specimens, including consent requirements for various types of research. In addition to ethics committee oversight, there must be well-documented routines for coding and storage of tissues that promote the safety and personal integrity of sample donors. The expressed wish of patients that their sample not be used for scientific research should be respected. Permanent anonymization was not recommended because of the risk to scientific validity.

Although we do not disagree with these principles, the framework provided does not sufficiently address privacy risks associated with genetic research and does not define conditions for recontact in the event that consent is required. We propose a framework (Fig. 1) to better guide researchers and ethics committees that reflects the following principles:

1. The primary objective of ethics committee oversight is to balance the relative benefits of the research project and the risks, including privacy risks and any other risk of harm.
2. To preserve the capability to validate data and to preserve scientific integrity, the source data file should not be anonymized. Rather, the source data should be coded (linking each sample to its donor). These data must be protected by encryption and file protection on a password-protected, nonmobile computer or in a locked filing cabinet.
3. Risks to privacy must be assessed. When risks are minimal and reconsent impracticable then a waiver of the requirement for informed consent may be granted.
4. Risks should be considered minimal when samples/data are shared in databases that are restricted to bona fide researchers with a legitimate research purpose, data access requests are reviewed for their scientific merit and ethical acceptability by an independent review board,

investigators who access the data agree to protect donors' privacy and maintain their confidentiality, the proposed research is not inconsistent with the original consent (when there is one), and the proposed research is not potentially stigmatizing or sensitive to an individual or a group, as judged by the independent ethics review board.

5. Factors that should be considered in determining whether recontact is impracticable include: the likelihood that the researcher has current contact information; the probability that the patient is alive and not incapacitated; the probability of harm to the patient in recontacting them; and the expense and time anticipated to recontact, as balanced with the likelihood of success.
6. If risks to privacy are considered greater than minimal risk, then recontact for informed consent should be required. That is, to protect the greater privacy of the participant, a small infringement in privacy consisting of recontact for the purpose of securing informed consent is justified. The value of the biomedical information gained may also be considered.
7. In many instances, risks to privacy and risks of stigmatization cannot be accurately estimated or anticipated. This is particularly true when archival samples collected for one purpose are used for a secondary purpose that was not anticipated at the time of collection, as in the Havasupai case. Therefore, the tenets of the Precautionary Principle may be invoked.[24,25] That is, a (preventive) consent requirement should be considered in the face of uncertainty. Participant preferences and attitudes toward consent and disclosure support a consent requirement in any instance of uncertainty.[37,38]
8. Data derived from unconsented patients should never be shared in a publicly accessible database. It may be permissible to share data in a database with controlled access. However, any future access to information or tissue from such a database mandates review by an ethics or data access committee.
9. Security procedures for the collection, transmittal, and storage of information should be commensurate with the sensitivity of the information recorded. Personal information recorded should be directly related to the stated research activity. Clinical follow-up that requires recontact represents a greater than minimal risk to privacy.

Archival tissues remain a rich source of human tissue for translational research. Given the potential value of biomedical information derived from such tissue, any ethical framework for accessing these tissues should not be obtrusive to researchers. Conversely, the rights of participants and risks to them, largely comprised of privacy risks, must be considered. Informed consent should generally be required, but the requirement for informed consent can be waived if an ethics oversight committee determines that the risks to subjects are minimal and reconsent would be impracticable.

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