

Editorial

Ethical, Legal, and Policy Issues: Dominating the Biospecimen Discussion

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With over 300 million human specimens currently stored in the United States, biospecimens are invaluable to the scientific research community. In addition to technical considerations related to the physical quality of a biospecimen, multiple ethical, legal, and policy issues also affect the ability of researchers to use these resources. The National Cancer Institute (NCI) Best Practices for Biospecimen Resources was developed in response to the results of an internal NCI study that found considerable variability in the procedures and guidelines used for biospecimen resource management across NCI facilities. The study also revealed that some of the primary sources of variability were divergent approaches to ethical, legal, and policy issues. The NCI Office of Biorepositories and Biospecimen Research was established in 2005 to address these issues, resulting in publication of the First-Generation Guidelines for NCI-Supported Biorepositories in April 2006. Following a public comment period, the document was revised and renamed the NCI Best Practices for Biospecimen Resources (NCI Best Practices) and is available on the NCI Office of Biorepositories and Biospecimen Research Web site (1). This editorial describes some of the key ethical, legal, and policy issues related to the use of biospecimens in research. Although the NCI Best Practices attempts to address some of these issues, many remain unresolved and will require further discussion among stakeholders within the biospecimen research community. The Office of Biorepositories and Biospecimen Research has been engaged in such discussions through its involvement in an AACR panel discussion at the 2007 annual meeting and more recently through sponsorship of a workshop on biospecimen custodianship.

Biospecimens in the News

In the past year and a half, ethical issues related to biospecimens have produced headlines in the New York Times on three separate occasions (2-4). The topics of these stories have ranged from chronicling the status of "ownership" of biospecimens over the last 20 years (2) to

outrage from indigenous peoples who feel their blood samples were not properly consented and were used inappropriately (3). The case of *Catalona v. Washington University*, relating to biospecimen ownership, was covered in the scientific and popular press (5). In March 2006, a Missouri judge ruled in favor of Washington University, stating that the institution rather than the researcher or the patient owned the biological samples under dispute, which had been contributed for research purposes. This decision was subsequently upheld on appeal. In a separate case, an Arizona Native American group that had donated biospecimens for diabetes research raised concerns that the biospecimens also were being used for other unspecified uses, such as schizophrenia research (6). And there were objections to a National Geographic Society project in which DNA markers collected from Native Americans were to be used to study human migration patterns (4).

These court cases and recent interest in the popular press underscore the importance of developing new policies and standard practices in biospecimen-based research, particularly with respect to ethical and legal areas. Five major topic areas are addressed in the NCI Ethical, Legal, and Policy Best Practices: (a) principles for responsible custodianship, (b) informed consent, (c) privacy protection, (d) access to biospecimens and data and, (e) intellectual property and resource sharing. The public comments received by NCI and the media reports and court decisions outlined above show that there are several unresolved issues that are not addressed in the current NCI Best Practices or other guidance documents.

Custodianship and Ownership Issues

From a legal standpoint, few cases or studies directly address the ownership or custodianship of biospecimens (7), and there are no laws or regulations that directly address these issues. Although regulatory guidance and best practices exist, they do not have the force of law and, therefore, are not used as the basis for court rulings. Current judicial precedent is to settle such cases using common law property theories or the elements of a donation under a state's gift law. This precedent was set nearly 20 years ago in the landmark *Moore v. Regents of the University of California* case (8) in which the California courts determined that the plaintiff's specimen donation was a "gift" to the institution, and therefore, he could not lay any claim to the financial benefit derived from research using his biospecimen. This is, of course, problematic as human specimens may not clearly fall under

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the same category as other gifts. Nevertheless, courts continue to rely on this precedent for rulings today. Specific issues relevant to biospecimen donation that have not been addressed by common law include the following: What conditions are appropriate to place on the contribution of biospecimens to research, for example, does gift law allow a gift with conditions? How does the decision of a research participant to discontinue their participation in the study, often offered in informed consent forms, affect the status of the gift? What if it is the practice of an ethnic or cultural group to have their specimens returned? What if a patient needs their specimen back for a purpose that may be beneficial to their health or the health of their family?

In addition to these legal issues, patients are becoming increasingly aware of the importance of their biospecimens to research, and some patients and advocacy groups have developed biobanks to support research into their disease of interest (9, 10). However, there currently are no formal systems in place for interacting with patients about biospecimen research, and misinformation abounds. For instance, patients may believe that their biospecimens are freely shared within the research community when this is not always the case. Based on informal discussions with patient groups, advocates are particularly concerned about privacy issues (11), biospecimen sharing, the use of biospecimens for commercial purposes, and the return of research results.

Future and Secondary Uses of Biospecimens

Do investigators have an ethical obligation to patients beyond the time at which they donate their biospecimens (12), even though the courts have decided that the patient relinquishes their rights to the biospecimens once they are donated (5, 8)? Studies suggest that patients are willing to contribute their biospecimens to research as long as the specimens are used appropriately and new information is being gathered from investigations (13). Investigators often collect and store biospecimens for future use awaiting the development of new techniques or for further investigation of interesting findings. Many would say that investigators have an obligation to inform patients if studies using their biospecimens are dependent on funding and their biospecimens are being stored for potential future research.

Because some patients may object to their specimens being stored indefinitely for unknown future research, informed consent may be needed for both a particular use as well as for banking of the biospecimens for future research. There is also the question of whether specimens should be shared with, for example, pharmaceutical companies for unspecified research. Some institutions have chosen to make the distinction that future unspecified use by profit-making institutions would not be in the best interests of the patient or the biospecimen resource. However, preventing patients from enrolling in a clinical trial because they have not consented to future, unspecified use of their biospecimens could be considered coercion. Given the distinction between obtaining biospecimens for a research study and saving material for future, unspecified use, separate Institutional Review Board approval may be required. Research groups are

struggling to develop an acceptable informed consent document that covers broader aspects of disease and research. One option is for the patient to give line-item consent that allows access to their biospecimens for particular diseases. Surveys have found that a large proportion of patients surveyed would agree to having their biospecimens stored for future studies of unspecified medical conditions (13). The tension remains between being transparent with patients and preserving biospecimens for future unspecified research purposes.

The Informed Consent section in the NCI Best Practices includes a recommendation to consider tiered consent to allow participants to give permission for certain uses of specimens and not others. However, the Best Practices document also states that allowing such options requires the ability to track the specific research consented to by each patient. Another consideration for tiered consent is that researchers also must adhere to the requirements of states' genetic privacy statutes, which may require specific procedures that go beyond those used in obtaining informed consent for other types of biospecimen research. The National Conference of State Legislatures Web site (14) has compiled each state's privacy laws.

Consenting patients for future use of biospecimens is further complicated by the discrepancies between relevant federal regulations. Although 45 CFR 46 Subpart A (the Common Rule) allows consent of patients to future unspecified research, the Health Insurance Portability and Accountability Act Privacy Rule requires that each authorization by the patient for release of protected health information includes a specific research purpose. In addition, under the Health Insurance Portability and Accountability Act Privacy Rule, the creation of a biospecimen resource or database with protected health information and subsequent disclosures for research purposes are considered separate activities. Each activity requires authorization from the research participant unless a waiver or alteration of authorization is obtained from a Privacy Board or Institutional Review Board. Because support of future research is a major purpose of biospecimen resources, this lack of harmony among federal regulations has had a significant effect on, and created a great deal of confusion within, the biospecimen community. Some experts have even argued that many of the Privacy Rule provisions provide additional burdens on researchers that do not necessarily translate into greater protection of privacy for research participants (15, 16).

Cultural Issues Relevant to Informed Consent

Aside from the NCI Best Practices, there are several other guidance documents that have been published (17). The documents have different goals and approaches to ethical, legal, and policy issues that may create confusion in the research community as well as among different populations of study participants. Several issues, as noted among the list of high-profile news accounts, relate to the disposition of tissues from Native American populations. A 2005 study (18) addressed issues related to Native Americans and biospecimens. Native Americans have been made aware of the Moore case and generally disagree

with the California court's conclusion that donated tissues no longer belong to the study participant. This view is supported by the recent 8th Circuit opinion in the appeal of the Catalona case (19), which rests on a rigorous examination of the informed consent form and supporting documentation to determine the donor's intent at the time the gift was made. Investigators who plan to work with Native American populations to collect specimens for research need to be aware of beliefs and practices and to develop a relationship of trust with potential study participants. Study participants may want their unused specimens returned for burial or other religious ceremonies, and the informed consent must make clear whether this will be possible. State and federal biosafety regulations must also be considered when determining whether specimens may be returned to the participant. Native populations may be unwilling to consent to future unspecified research for fear that research may be done that would stigmatize their community. Recent perceived abuses, in which specimens from native populations were used without specific consent, have only heightened this fear. In addition, native populations are sensitive to the use of their specimens for the development of treatments by commercial entities. The perception is that such treatments are often too expensive and less available to native populations.

Next Steps

The purpose of the Ethical, Legal, and Policy section of the NCI Best Practices was to clarify how key regulations pertain to biospecimens and to suggest additional best practices for consideration that may go beyond expectations of existing regulations. The NCI's experience in developing and modifying the Best Practices shows that, although there are concerns in the research community about adoption of biospecimen technical and operational standards, the ethical, legal, and policy issues require considerably more discussion. Several domestic and international efforts are under way to address informed consent, privacy, ownership, and access issues with respect to biospecimen collection and use. However, state and local laws, differences in local Institutional Review Board approaches, and cultural practices can vary significantly. All of these factors must be taken into account in designing and implementing research studies involving biospecimens. The NCI is currently engaged in

efforts to bring together diverse groups in a series of workshops and public forums. In concert with other similar efforts, it is hoped that a series of new recommendations will emerge.

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