Custodianship and Ownership Issues In Biospecimen Research

Symposium–Workshop

Hilton Washington DC/Rockville Executive Meeting Center
Rockville, Maryland
October 4–5, 2007

SUMMARY

Office of Biorepositories and Biospecimen Research
National Cancer Institute
National Institutes of Health
U.S. Department of Health and Human Services

Prepared by:
Rose Li and Associates
May 2008

Table of Contents

Summary

I. Background

Biospecimens are critical to the development of new diagnostic, therapeutic, and preventive agents for patients with cancer, yet ensuring equitable and continuous access to these specimens remains a challenge. Individuals charged with the care and keeping of biospecimens often have competing interests regarding who owns the biospecimens, how the biospecimens are used, and who ultimately benefits from them. Variations among State statutes and ambiguity about the rights, roles, and responsibilities of various stakeholders have permitted some to profit from alleged abuses involving biospecimens in a lucrative and ever-expanding market for human specimens. Moreover, access to biospecimens has been impeded by the recent trend of biospecimen resources[1] and researchers stockpiling rather than sharing tissue samples, as well as by more aggressive patenting and licensing strategies for discoveries made from biospecimens

The present framework for organ and biospecimen donation began with the creation of the Anatomy Act of the United Kingdom in 1832. This act was created in response to the crimes of Burke and Hare, who murdered 16 people to sell the cadavers for dissection in anatomy lectures. The Anatomy Act allowed for the provision of cadavers from hospitals, work houses, and prisons *only* if the bodies were unclaimed, and it specifically prohibited trade in bodies. The rise of autonomy in American law and bioethics further shaped the public's attitude about the property status of the body. The emphasis on autonomy created the perception of self-determination; the idea of the right to control one's body; and the assumption that what one controls, one owns. When organ transplantation involving living persons emerged in the 1950s, it engendered heated controversy over its morality. It was decided that the best ways to protect people while maintaining consistency with the view of the body as sacred were to make organ transplantation voluntary, to have informed donors, and to remove the profit motive. The 1968 Uniform Anatomical Gift Act supported the requirement for informed and voluntary donation.

Unlike organ donation, ownership of biospecimens is still a matter of debate. Some argue that because of the many benefits arising from research using biospecimens, they should be treated as public goods, and consent and control by individuals who provide these materials should be of less concern. However, no one would make a similar argument regarding organs donated for transplantation; even direct life-saving use of human tissues has not brought about the creation of a moral framework under which biospecimens are treated as public goods. Voluntary, informed, altruistic gifting is likely to remain the ethical framework for the use of biospecimens in research, and policies developed by the National Institutes of Health (NIH) are not expected to vary from this paradigm.

[1] A biospecimen resource is defined as a collection of human specimens and associated data for research purposes, the physical structure where the collection is stored, and all relevant processes and policies. Biospecimen resources vary considerably, ranging from formal organizations to informal collections of materials in an individual researcher's freezer (*NCI Best Practices*, 2007).

Several other biospecimen custodianship and ownership frameworks have been proposed. In one such framework, individuals would be seen as contributors, not as donors, and biobanking would be based on managed control of biospecimens through custodianship as opposed to strict ownership. A trusted intermediary would manage and guide access and use of biospecimens, associated information, and research results. It has been suggested that this model comes closest to addressing the interests and meeting the expectations of all stakeholders involved in the biomedical research process. In another framework, the best policies are those in which the rights of the research participant are recognized. If the biospecimen is an outright gift, then its disposal should be under the control of the principal investigator or based upon institutional policies. If the biospecimen is a limited transfer, however, then the research participant should determine its final outcome.

Legal precedents related to ownership of biospecimens tend to be fact specific and jurisdiction specific, and decisions in such a small number of cases do not yield a robust body of law. To date, courts have denied claims of biospecimen ownership based on common law property or gift theories. Although courts have been sensitive to the public policy implications of interfering with the research process and potential harms to biomedical research, they have not fully considered the need to maintain trust and transparency in research to ensure future participation by individuals. In *Washington University* v. *Catalona*, the Federal District Court for the Eastern District of Missouri held that research participants do not retain any rights to control their biospecimens after donation.[2,3] The court stated that under the circumstances of that case, the donation of biospecimens was an *inter vivos* gift containing all the elements of donation: Donative intent, the giving of the gift, and the receiving of the gift. However, the court also implied that research participants have a continuing interest in their biospecimens. The key documents in this decision were the informed consent documents and an accompanying brochure. The court used those not as contracts but as evidence that the research participants did not retain the right to revoke and physically repossess the donated biological material nor retain the right to direct or authorize the use or transfer of destination of the biological material after their donation. However, in a later decision, the U.S. Court of Appeals for the Eighth District indicated that research participants do retain the right to discontinue participation in the research by doing any of the following: (1) not answering any additional questions; (2) not donating more tissue; and (3) disallowing the use of their tissue in future research. The District Court and the Court of Appeals adopted the public policy perspective that medical research can advance only if private agendas do not thwart access to donated biospecimens.

Even though the issue of biospecimen ownership remains to be resolved in the legal arena, research participants often expect that patient care has priority over the research use of biospecimens; that researchers adhere to the ethical principles, requirements, and personal choices specified in the informed consent document; and that researchers publish their results so that others can benefit from their findings. Research participants also expect that cultural and

[2] The term "research participant" is equivalent to the term "human subject" and refers to an individual, such as a patient or volunteer, who consents to being involved in research (National Cancer Institute Office of Biorepositories and Biospecimen Research working definition).
[3] *Washington University* v. *Catalona*. Case No. 4:03CV01065-SNL (ED Mo, filed August 4, 2003).

religious beliefs are considered in ownership and custodianship policies. For example, many Native Americans believe that the body is sacred and should not be disturbed. They also believe that if an individual gives an institution the right to use a portion of his or her body for research, that individual or his or her family can retract that right at any time, even after the individual's death. Thus, Native Americans and other groups with related religious or cultural beliefs may expect investigators to follow the instructions of research participants or their families regarding the disposal or return of the biospecimen. However, although research participants can exercise the right to discontinue participation in the future, the precedent set by *Washington University* v. *Catalona* is that research participants do not have the right to revoke and physically repossess donated biospecimens or to direct or authorize use or transfer of the material once it is donated, particularly if the initial donation meets all the elements of an *inter vivos* gift. Nevertheless, an informed consent document, a State law, or Federal research regulations—in another set of circumstances—may be interpreted to give the research participants that right.[4]

A. *National Cancer Institute Best Practices for Biospecimen Resources*

During the past several years, the National Cancer Institute (NCI) has undertaken an intensive due diligence process to understand the state of its funded biospecimen resources and the quality of biospecimens used in cancer research. These activities began in 2002 with surveys and community forums and continued in 2003 with the publication of the *National Biospecimen Network Blueprint* and *Case Studies of Existing Human Tissue Repositories.*[5,6] The NCI examined the state of its biospecimen resources in 2004. It then established the Biorepository Coordinating Committee and, later, the Office of Biorepositories and Biospecimen Research (OBBR) to lead and coordinate a strategic plan to address biospecimen issues. This included the organization of two 2005 workshops where representatives from the cancer research and advocacy community as well as ethics, legal, and policy experts discussed approaches to unify, integrate, and improve NCI-supported biospecimen resources. These efforts eventually resulted in development of *First-Generation Guidelines for NCI-Supported Biorepositories*, which was later renamed *NCI Best Practices for Biospecimen Resources* (*NCI Best Practices*).[7]

The *NCI Best Practices* provides salient guiding principles that define state-of-the-science practices, promote biospecimen and data quality, emphasize appropriate access to biospecimens, recognize the interests of research participants who provide biospecimens, and support adherence to ethical and legal requirements. However, the *NCI Best Practices* does not specify the custodial rights, roles, and responsibilities of biospecimen resource or their host institutions, investigators, and human research participants, and it does not offer a specific, functional definition of

[4] See, for example, *York* v. *Jones*, 717 F, Supp. 421, 426–27 (ED VA 1989).
[5] National Cancer Institute, Office of Biorepositories and Biospecimen Research. National Biospecimen Network Blueprint. Available at http://biospecimens.cancer.gov/biospecimen/network/. Accessed May 5, 2008.
[6] National Cancer Institute, Office of Biorepositories and Biospecimen Research. RAND Report: Case Studies of Existing Human Tissue Repositories. Available at http://biospecimens.cancer.gov/biospecimen/network/rand/. Accessed May 5, 2008.
[7] National Cancer Institute, Office of Biorepositories and Biospecimen Research. NCI Best Practices for Biospecimen Resources. Available at http://biospecimens.cancer.gov/practices/. Accessed May 5, 2008.

custodianship.[8] The document does not address the nuances of cost recovery and transfer of biospecimens, nor does it provide recommendations related to access to biospecimen-derived products and benefits.

B. Symposium–Workshop on Custodianship and Ownership Issues in Research Using Biospecimens

On October 4–5, 2007, the NCI OBBR held a symposium–workshop to define the parameters of custodianship that would allow biospecimen resources to operate in a culture of transparency, fairness, and accountability to all stakeholders. (For more information on this symposium–workshop, please visit http://biospecimens.cancer.gov/practices/caoissues/.) After keynote and plenary presentations from a variety of stakeholders and experts, workshop participants joined breakout groups to address specific questions and revise or generate specific recommendations in the realm of custodianship and ownership issues. These groups addressed the following topics: (1) Considerations for research participants, investigators, and institutions; (2) financial conflicts of interest (COIs); (3) intellectual property (IP); and (4) access to products and benefits. Breakout group chairs presented to meeting participants their panels' recommendations, conclusions, and issues for further discussion. The remainder of this summary highlights new or revised recommendations regarding custodianship as well as issues that will need further discussion following the symposium–workshop.

II. Considerations for Research Participants, Investigators, and Institutions

A. Areas of General Consensus

1. *Elements of the Informed Consent Document*

Discussants stressed the desire to have a clear and concise informed consent document that outlines the most important issues and risks using straightforward language. Regarding the specific information that should be provided to research participants, discussants listed the elements described below.

Biospecimen Resource Governance. Research participants need to understand the biospecimen resource's governance at the level of basic oversight, rules, and guidelines. Governance consists of the set of authorities, processes, and procedures—including particular risk-benefit ratios—guiding key operational decisions made within the biospecimen resource. Governance affects access and research use decisions and custodial relationships and responsibilities. Discussants recommended including, as part of the informed consent supplementary material, a one-page document with a graphical summary of the biospecimen resource's governance, with an

[8] The NCI has chosen to use the term "custodianship" rather than "ownership" in the context of human specimens because issues of ownership have yet to be resolved effectively in statute, regulation, or case law. Specifically, "custodians" are people who are entrusted with the managed control of biospecimens. The NCI's rationale for using the word "custodianship" is based on the distinction between the definitions of custody and ownership. Custody suggests immediate charge and control as well as responsibility for the protection and preservation of the object or entity in custody. Ownership, on the other hand, suggests final, absolute control and the ability to do what one pleases without accountability to anyone else.

emphasis on oversight of the biospecimen resource and access to its collection. Several attendees suggested that the governance information also should be part of a general "custodianship plan," which could be made available upon request in a separate communication (see Issues for Further Discussion below).

Benefits and Risks of Research Participation. Research participants need to know which particular biospecimens are being sought and why they are being asked to participate in the study. Some participants also may want to know whether participation will benefit—or even potentially negatively impact—their families and communities. Because the risk of stigmatization and discrimination based on research results may be high for some groups, it is important that they be made aware of these risks through the informed consent document. Such research participants may wish to know whether family members will be required to join—or be automatically excluded from—the same or similar research. The source of the biospecimens to be used also should be indicated. For example, research participants need to be told whether the biospecimen will come from leftover tissue from a surgical procedure or from tissue excised for research purposes during a special procedure. Finally, in the areas of cancer investigation and genetic research, research participants should be given several days to review informed consent documents before signing them. With many medical procedures, there is often little time for reading, reflecting upon, and discussing the informed consent document before a research participant is asked to sign it.

Biospecimen-Associated Data. Research participants should be informed about the type of data that will accompany the biospecimen. In addition, they should be told whether the biospecimen-associated data will be snapshot or longitudinal data,[9] and they should be well informed about the data's degree of identifiability.

Primary Versus Secondary Research Use.[10] Research participants should be asked whether their biospecimens can be used in secondary research and must be given sufficient information to make such a decision. If their biospecimens will be used for genetics research, they should be informed whether somatic, familial, or whole-genome analysis will be conducted. Knowledge of the specific type of genetics research to be conducted affects the risks and considerations participants must weigh. Discussants agreed that research participants need to be informed when their biospecimens are going to be deidentified and used for other research purposes without specific consent.

Reporting of Research Results. Research participants need to know whether they should expect to be contacted with research results or new research protocols. The form of communication (e-mail, newsletter, or phone call) should be specified, with the procedure for opting out of all communications clearly indicated.

[9] "Snapshot data" refers to clinicopathological data at diagnosis. "Longitudinal data" refers to treatment and outcome data.

[10] "Primary research" refers to the research that is directly related to the study as described in the informed consent form. "Secondary research" refers to any other research use beyond the scope of the primary study.

Biospecimen Storage and Disposal. Research participants should understand that biospecimens will continue to be stored and shared as long as they are potentially useful for research. They should understand how biospecimens that are no longer useful are disposed of and whether they will be notified before such disposal. Those who authorize being recontacted via the informed consent document and for whom updated contact information is maintained should be notified before contributed biospecimens are transferred to another accredited resource or respectfully destroyed. Finally, research participants with religious or cultural requirements around the disposal of biospecimens should be given a timeframe within which their specimens can be returned to them.

Additional Information. Some research participants may want more information than can be easily presented in a one-page informed consent document. For these interested participants, more detailed supplementary materials and brochures should be made available.

> **Recommendation 1.** For the benefit of research participants, a one-page informed consent document outlining important issues and risks in straightforward language should be developed and implemented. The document should specify the following:
>
> - Why particular biospecimens are being sought—i.e., why research participants are being asked to participate;
> - Who will be the "custodian" of the biospecimens;
> - Whether research participation could benefit or potentially negatively impact participants' families and communities;
> - What is the source of biospecimens to be used;
> - How the biospecimen will be used and whether it will be used for secondary research as well;
> - What type of data will accompany the biospecimen and whether the data will be identifiable;
> - Whether research participants should expect to be contacted with research results or new research protocols;
> - That biospecimens will continue to be stored and shared as long as they are potentially useful for research;
> - That if biospecimens are no longer useful, research participants who authorized being recontacted via the informed consent document and for whom updated contact information is maintained will be notified before contributed biospecimens are transferred to another accredited resource or respectfully destroyed; and
> - That inventions may arise from research using biospecimens and what benefits, if any, the participant would receive (see Recommendations 10 and 15).

Recommendation 2. In addition to the informed consent document, more detailed supplementary materials should be made available to interested participants. These materials may include the following:

- A one-page graphical summary outlining the biospecimen resource's governance with an emphasis on oversight and access protocols; and
- An accompanying brochure that provides more detailed information.

2. *Cultural Issues in Informed Consent*

Personal, religious, and culturally held beliefs and traditions always should be respected in biomedical research using biospecimens. For example, there is a belief held among many Native Americans that the body is sacred and should not be disturbed. Members of the Orthodox Jewish community believe that the body must be buried whole. Investigators should consider the beliefs of the community when planning a research study that will collect biospecimens. During the consent process, investigators should consider whether to ask research participants about cultural issues, including the following:

- Whether there are any religious, cultural, or personal restrictions regarding the biospecimen;
- Whether they want their family to have any rights to the biospecimen;
- What are the instructions for disposal or return of the biospecimen; and
- What is the participant's primary language and whether the consent was explained in that language.

3. *Selection of a Custodian*

There was general agreement that, in the ideal case, custodians should be separate from investigators. However, discussants recognized that in some cases complete separation would prevent biospecimen resource personnel from contributing to research efforts. All agreed that when the investigator is the primary holder of the biospecimens and data, he or she should have the same duties of custodianship and abide by the same ethics that apply to research use. Thus, biospecimens in small collections held by investigators should be collected, stored, and distributed with the same oversight and quality-control mechanisms applied by traditional biospecimen resources.

Discussants agreed that if investigators are going to use and store biospecimens for research beyond the scope of the initial consent and collection, they should be encouraged to establish or join an existing institutional review board (IRB)–approved and regulated biospecimen resource. Such consolidation may help ensure baseline quality standards for smaller, grant-supported biospecimen collections. It also would decrease COIs experienced by investigators in the dual roles of research investigator and biospecimen resource manager. Discussants recognized that such a recommendation would require additional financial resources to establish new biospecimen resource "cores" or expand the biospecimen resources already within institutions.

Recommendation 3. In the ideal case, the custodian of the biospecimens should be someone other than the investigator. To this end, investigators with small biospecimen collections should be encouraged to establish or join an existing IRB-approved and regulated biospecimen resource. The NCI should consider providing the necessary financial resources for this type of consolidation.

4. *Legacy or Contingency Plans for Biospecimen Resources*

During transitions or following a loss of management or funding for a resource, an assessment should be made as to whether the stored biospecimens still have value for research. If stored biospecimens do have research value, the biospecimen resource should attempt to become financially self-sustaining or transfer its collections to similarly accredited research facilities. Biospecimen resources should use the same decisionmaking criteria for allowing transfer of biospecimens to other qualified resources as they do when allowing transfer of biospecimens to investigators.

Recommendation 4. Biospecimen resources should have legacy or contingency plans that address the transition following the loss of management or funding. These plans should involve an assessment of whether the stored biospecimens still have value for research. If a resource's stored biospecimens do have research value, the resource should attempt to become financially self-sustaining or transfer its collection to similarly accredited research facilities. Biospecimen resources should use the same decisionmaking criteria for allowing transfer of biospecimens to other biospecimen resources as they do when allowing transfer of biospecimens to investigators.

5. *Gaining and Keeping the Public's Trust*

Public trust is important for biomedical research using biospecimens. Research participants and biospecimen contributors must trust that their privacy and autonomy will be honored, that promises made to them will be kept, and that their gift of biospecimens will advance health care and be of benefit to the general public. Taxpayers must trust that their income tax dollars will be used wisely. Increasing and maintaining public trust requires transparent policies and accountability as well as individual and community involvement in education, oversight, and feedback. It is therefore important to reach out to individuals and the community with educational efforts to increase understanding of the research enterprise, biospecimen resources, and research using biospecimens. Individuals and communities should take an active role in oversight at biospecimen resources, expressing any concerns that may arise. The NCI should encourage the inclusion of institutional ownership and custodianship policies in clear and concise informed consent documents.

Recommendation 5. Biospecimen resources should act as trusted intermediaries and custodians of biospecimens provided for research. In this role, they should demonstrate the accountability needed to promote public trust by accepting all of the custodial responsibilities listed below and, as appropriate, establishing independent advisory boards—including research participants among the active members—to accomplish them:

- Implementing overall operational, ethical, and legal policies based on feedback from individuals and the community;
- Ensuring appropriate scientific assessment, access decisions, and management of COIs;
- Making decisions related to the descriptions, publications, and dissemination of research results that are potentially stigmatizing or discriminating to groups; and
- Educating the public and obtaining their feedback.

B. ISSUES FOR FURTHER DISCUSSION

1. *Biospecimen Ownership and Informed Consent*

Informed consent documents typically do not directly address the issue of biospecimen ownership either by the research participant who provides the biospecimen, the investigator, or the institution housing the biospecimen resource. The ambiguity surrounding ownership rights in some cases has led to a failure in meeting informed consent requirements (i.e., to provide a participant in federally funded research all material information needed to make a reasoned and informed decision on whether to incur certain risks by participating in a research study).

2. *Template Custodianship Plans*

Although discussants did not reach consensus about the required elements of a template custodianship plan, they suggested the following content:

- How the integrity of the biospecimens and associated data is maintained and monitored;
- How the rules of access and distribution of biospecimens are defined;
- What roles and responsibilities the biospecimen resource and its employees have;
- What legacy or contingency plan, if any, the biospecimen resource has in place; and
- What circumstances, if any, allow withdrawal or transfer of biospecimens,

3. *Right To Withdraw From Research*

Discussants agreed that the term “withdrawal of consent” would be better framed as “termination of biospecimen use for research.” What should happen to biospecimens when research participants exercise their right to terminate biospecimen use for research is not clear. Suggestions included the following: Permitting research participants to withdraw or transfer any biospecimens stored in the resource, for any reason; allowing research participants to terminate use only for future research projects involving unused specimens; and preventing research participants from withdrawal or transfer of any biospecimens after they are distributed for research purposes. Discussants agreed that at a minimum, termination of use means stopping research involving any unused biospecimen(s) that remains at the biospecimen resource. They also agreed that if residual samples will be used for diagnostic studies, they should be collected, stored, processed, and tracked using a Clinical Laboratory Improvement Amendments–compliant method. Discussants did not resolve whether participants should be allowed to transfer biospecimens between facilities. Some discussants suggested that such transfers would lead to a chaotic research environment, while others suggested that participants should be allowed to use

biospecimen transfers to take advantage of specialized medical care, new therapies, or innovative research projects.

4. *Privacy Risks and Concerns Among Research Participants*

Discussants considered the issue of whether new information technology systems, such as databases with permissions-based access, mitigate some of the privacy risks for individual research participants and groups. One view expressed was that research participants generally are not asked to allow their complete genomic sequence to be posted on a Web site for broad public access. In addition, researchers themselves can gain access to data only through a data access committee or similar structure. This view was challenged by other discussants, however, who pointed to the difficulties in ensuring complete anonymity if genetic sequences are made available. Concerns were voiced over the potential for particular research outcomes to lead to the stigmatization of or discrimination against research participants or groups. All agreed that these risks must be carefully weighed and balanced against the potential benefits offered by research using biospecimens.

III. Financial Conflicts of Interest

A. Areas of General Consensus

1. *Disclosure of Financial Conflicts of Interest*

Biobanking activities may be sufficiently unique to require COI policies beyond those considered acceptable for other grants and contracts. Most breakout group discussants supported a requirement for higher standards in biobanking operations. One way to handle financial COIs is through prohibition. For example, investigators could be prevented from accepting unreasonable cash compensation or from holding substantial equity positions in companies funding their research. Investigators who may have a vested interest in a study also could be prohibited from asking patients for consent to participate in such research. Another way to manage COIs is by disclosure. The latter method was deemed more reasonable by discussants as long as the financial conflicts that lend themselves to bias are not so great that mere disclosure is insufficient to eliminate the possibility of that bias.

Discussants agreed that it may be reasonable to place the COI management burden on the existing institutional COI infrastructure rather than on individual investigators or IRBs, as is currently the practice with human subjects research. The challenge with internal regulation, however, is assuring that consistently rigorous regulation is applied from one institution to the next, particularly in cases where the institution may benefit financially from a relationship with an external party. Further, information on internal regulation across institutions is not readily available to the public.

> **Recommendation 6.** The term “conflict of interest” should be more clearly defined. Additionally, existing institutional and NIH COI policies as they relate to biospecimens should be reviewed to determine whether they are sufficient and, if not, what areas remain to be addressed**.**

> **Recommendation 7.** Rather than require COI reporting in grant applications, investigators should adhere to institutional and NIH policies around COIs. Individuals required to report COIs should include all those who make decisions regarding biospecimen distribution or prioritization of acquisition, and information on financial COIs should be made publicly available.

Discussants agreed that institutional policies on the sharing of samples with other investigators or companies and financial implications of such sharing should be disclosed in informed consent documents. They also stressed the importance of presenting COIs concisely and clearly in informed consent documents to ensure accessibility. However, questions remained regarding the required granularity and mechanisms of reporting to the NCI in grant applications.

> **Recommendation 8.** Financial COIs, institutional policies for sharing samples with other investigators or companies, the financial implications of sharing, and any known or likely benefit to the institution or investigator should be disclosed in the informed consent document in a clear and concise manner.

2. Cost Recovery and Other Biospecimen Resource Sustainability Models

The *NCI Best Practices* recommends that "charges for samples, if any, are used only to recover reasonable costs associated with operation of the biospecimen resource" and supports a cost-recovery model. However, cost recovery alone may not be sufficient for a biospecimen resource to maintain its resources for an extended period of time. Moreover, different biospecimen resources, either nonprofit or for-profit, may follow different accounting guidelines and establish different pricing scenarios, which in turn may affect accessibility to biospecimens and data.

Discussants recognized that no single cost-recovery model would suit every biospecimen resource. Standardized formulas for cost recovery may not account for individual differences in financial reporting. There also was agreement that all commercial activities should be designed to foster widespread access to biospecimens. Furthermore, biospecimen resources in possession of biospecimen-associated clinical data that can be shared should be encouraged to do so.

> **Recommendation 9**. When addressing appropriate models of biospecimen resource sustainability, language in the *NCI Best Practices* should emphasize accessibility to biospecimens and data and sustainability of the biospecimen resource within a framework that maintains public trust. Furthermore, biospecimen distribution models other than cost recovery may be more able to sustain a biospecimen resource over the long term and should be considered.

B. ISSUES FOR FURTHER DISCUSSION

1. *Reporting Financial Conflicts of Interest in Grant Applications*

Although, ideally, grant applications submitted for funding by individual investigators and biospecimen resources should include information on potential COIs, discussants recognized that capturing all COI information in a grant application could be cumbersome, as conflicts may be myriad and change over time. In addition, the administrative burden of reviewing information on COIs may prove excessive for IRBs and peer review panels. Moreover, grant applications are not easily accessible to the public, which limits the transparency needed to promote public trust.

Ultimately, consensus on the issue of reporting financial conflicts of interest in grant applications was not reached.

2. *Reporting Mechanism and Management of Conflicts of Interest*

How COIs should be reported and who should be responsible for managing and reporting them are not clear. Discussants considered whether COIs should be reported periodically; who should determine what constitutes a COI; how differences of opinion among peer review group members would be managed; who should evaluate COIs to determine whether conflicts preclude funding; and whether the burden of ensuring there are no COIs should fall on investigators, IRBs, or the institution. Discussants also considered who would manage and report any new COIs that arise (e.g., from the transfer of oversight or ownership of biospecimens), who would receive such reports, and what mechanisms would be used for reporting in the event of new COIs. The role of audits in these processes is not clear.

3. *Additional Conflict-of-Interest Information Resources*

In addition to the above recommendations and issues for further discussion, several existing COI information resources will inform future versions of the *NCI Best Practices*, including the November 2001 U.S. General Accounting Office report entitled "HHS Direction Needed to Address Financial Conflicts of Interest," Office for Human Research Protections COI guidance, and the NIH Guide "Objectivity in Research."[11] In light of current financial COI policies in biomedical research, additional, unique challenges that biospecimen resources may encounter will be carefully considered.

4. *Application of Appropriate Biospecimen Resource Sustainability Models*

Discussants were unable to reach consensus on the circumstances under which commercialization of biospecimens and associated data is appropriate. Furthermore, although it was recognized that biospecimen distribution models other than cost recovery (e.g., for-profit model) may be more able to sustain a biospecimen resource over the long term, specifics about these models and circumstances under which they would be appropriate remain to be established. Other issues for further discussion included whether a description of biospecimen resource sustainability processes should be required in grant applications, what constitutes full costs and whether these costs should include maintenance, who would evaluate and what criteria would be used to evaluate a proposal on a sustainability model, and whether existing models of independent assessment of stewardship is germane to biospecimen banking; e.g., the four-star rating system used to assess a nonprofit organization's use of fundraising expenses.

[11] These documents are available in electronic form at http://grants2.nih.gov/grants/policy/coi/resources.htm.

IV. Intellectual Property

A. Areas of General Consensus

1. *Ownership of Intellectual Property Derived From Research on Biospecimens*

The successful commercialization of technologies derived from research using biospecimens may require IP protection to lower investment risk. However, IP policies and strategies should be balanced with the need to promote equitable and continuous access to biospecimens within the research community. A key to fostering rapid scientific progress and commercial development is developing and implementing IP policies that promote wide access to research resources (i.e., biospecimens) and the development of biomedical products for clinical use (i.e., therapeutics and diagnostics) while maintaining public trust through accountability, transparency, and justice.

One controversial issue involves determining who should own the IP related to inventions resulting from the use of biospecimens. By law, the inventor or assignee has ownership rights, but one could argue that both research participants and biospecimen resources could acquire rights by other mechanisms, giving them the ability to influence patenting and licensing decisions on inventions or discoveries arising from research using biospecimens. Some argue that giving research participants equal ownership rights over the biospecimens would give each individual participant the right to block patents and associated development of the invention or exploit financial gain without involving other participants. Others argue that giving individuals who provided the biospecimens (or the individuals' organizational representatives) a right to influence licensing decisions will guarantee that a single institutional patent holder does not prevent other researchers from making any use of the patented invention (e.g., a genetic sequence) in research. If research participants will not be permitted to influence patenting and licensing decisions for inventions arising from research on their biospecimens, that information needs to be specified in the informed consent form, along with information about the implications of commercialization. An individual or group may prefer to participate in a study where inventions are not patented by investigators and biospecimen resources or where inventions are patented but can be freely used by other researchers.

The question of whether biospecimen resources should have IP rights related to the biospecimens they store and manage should be negotiated by the parties involved. The current *NCI Best Practices* employs language that allows for flexibility on this issue. As per the *NCI Best Practices*, both research participants and biospecimen resources should be made aware that they are not necessarily entitled to receive royalties from downstream products derived from research using biospecimens. Given that the American Medical Association Code of Ethics allows investigators to share commercial benefits from research using biospecimens with the tissue source, research participants may expect such sharing.[12] To further clarify these issues, the NCI should aid in the development of educational materials covering relevant topics in IP as applied to research using biospecimens.

[12] American Medical Association. *Code of Medical Ethics: Current Opinions with Annotations, 2000-2001*. Chicago: AMA, 2000.

Recommendation 10. The informed consent document should clearly state whether any financial benefits that result from commercial products arising from research with biospecimens will be shared with or under the control of the research participant from whom the specimen was derived.

Recommendation 11. The NCI should develop educational materials for potential research participants on IP issues in research using biospecimens. These materials should provide explanations for topics such as patents, licensing, commercialization, and the controversy involving the patenting of products of nature (see Issues for Further Discussion below).[13]

2. *Licensing Intellectual Property Derived From Research on Biospecimens*

When significant investment of time and resources is needed for commercialization, an exclusive license to the IP often is necessary and appropriate. However, exclusive licenses that grant overly broad, exclusive rights—for example, permitting a single licensee control of all fields of use or not permitting the grantor and research community to retain a research use license—can limit research and squelch the development of new uses of the licensed technology. Academic institutions should make research tools and unique biospecimen resources as broadly available as possible through the granting of nonexclusive research use licenses. Such an approach is in keeping with universities' research and educational missions. It also satisfies the need for peer-reviewed scientific journals to ensure that published data and conclusions can be verified by other researchers. By reserving IP rights in all fields of use, universities can ensure that inventors (for-profit and nonprofit) can conduct future research using protected and licensed technology at little or no cost.

Recommendation 12. When IP resulting from biospecimen research is exclusively licensed, a research use license should be retained that allows nonprofit and Government research use and ensures access to resources and data for research and educational purposes.

3. *Biospecimen Information and Data Sharing*

According to the NIH 2003 data sharing policy,[14] "research and resources should be made available no later than acceptance for publication." However, the ability to obtain IP protection outside the United States requires filing a patent application prior to public disclosure of research results through publication. In the United States, researchers have a period of 1 year to file a patent application from the point their data and results are disclosed. Within limits, delaying the

[13] It is a principle in patent law that a product of nature cannot be patented. Hence no patent is granted on any chemical substance of a definite and constant composition, even though it may, at the time when the patent was applied for, not yet have been found occurring ready formed in nature, but have been produced up to this time only by synthesis. Any process not previously known or used by which such products of nature can be produced is patentable. *Bulletin of Pharmacy*. 1897;XI:307-309.

[14] U.S. Department of Health and Human Services, National Institutes of Health, Office of Extramural Research. NIH Data Sharing Policy. Available at http://grants.nih.gov/grants/policy/data_sharing/. Accessed May 5, 2008.

release of research data for a definite period of time in pursuit of experimentation sufficient to qualify for IP protection eligibility is an acceptable practice.

Research consortia or "data clubs" can provide a means to increase biospecimen data sharing. Typically, members are required to deposit biospecimens and associated data as soon as possible, but other members of the consortium cannot publish on the data until 9 months later. The time delay provides an incentive for the original researcher to obtain an initial publication. For other members of the consortium, the data are accessible and help to direct—and may even accelerate—research.

The existence of a biospecimen resource, as well as restrictions on accessibility to stored biospecimens, should be made public when research data resulting from the use of those biospecimens are published. Generally, a publication includes information on how the biospecimens used were obtained so other researchers can obtain the same material and validate the research. If a limited resource is used, it should be made clear that the biospecimens are not available to others.

> **Recommendation 13.** In accordance with NIH policy, completed datasets and resources should be released as soon as possible and should be retained only as long as necessary for legitimate and imminent research purposes. A reasonable delay to ensure an investigator's publication priority or to secure IP protection is acceptable. Additional discussion will be needed to specify a finite time period after which NIH-funded researchers should disclose their data. The recommendation also applies to clinical data (e.g., disease diagnosis) if the biospecimen resource has these data and such data can be shared.
>
> **Recommendation 14.** The existence of biospecimens should be made public when research data resulting from the use of those biospecimens are published, even if the biospecimens themselves are not available to the research community.

B. Issues for Further Discussion

1. *Patenting Products of Nature*

The issue of whether the U.S. Patent and Trademark Office should continue to issue patents on certain kinds of genes, cell lines, proteins, or biochemical mechanisms has come under scrutiny and criticism by some scientists, legal experts, and policy analysts. First, this practice threatens the free dissemination of information that underlies basic science and academic research, and second, some biochemical derivatives of naturally occurring genes and proteins may differ insignificantly from unpatentable products of nature. Divergent views were expressed on when a discovery is an unpatentable product or law of nature versus an invention that meets the statutory requirements for patentability, an issue that remains to be resolved in the legal arena. Furthermore, while the NCI generally supports patent policies and strategies that lead to greater accessibility and free dissemination of information and research resources, the agency is not in a position to address the intricacies of what constitutes patentable subject matter.

V. Access to Products and Benefits

A. Areas of General Consensus

1. *Biospecimen Research Educational Efforts*

The NCI should use the media and its own publications to educate the public about its expectations regarding research using biospecimens, how the Institute oversees such research, and what financial or nonfinancial benefits, if any, research participants can expect from this research. Likewise, research participants' and contributors' expectations should be defined in advance of any study using biospecimens. Instead of developing best practices to address research participants' rights to developments arising from their specimens and/or data, the NCI should produce a template or brochure that outlines how the Institute oversees research using biospecimens and clearly defines and communicates to research participants what specific benefits, if any, they can expect from this research. This brochure should be considered an element of the informed consent process and an expression of ultimate respect for participants' autonomy.

2. *Benefits of Participation*

Research participants and their families should be informed that research results derived from their biospecimens may lead to commercial products. However, simply presenting the possibility of commercial product development to the research participant in the informed consent document is insufficient. Although the information need not be detailed and specific, an open dialogue between the individual administering the informed consent and the research participant should be part of the process. Such two-way communication provides the best opportunity for ensuring that research participants understand what is involved in the particular research study, who funds the study, and whether research using their biospecimens may lead to products benefiting the public.

The informed consent document should indicate how "reasonably foreseeable" future profits will be allocated. For example, the informed consent document might state that research participants will not share in any profits related to research. Alternately, it could indicate in a clearly defined manner how profits will be dispensed. Profits might be directed toward patient education, for instance, or toward a research foundation.

> **Recommendation 15.** Clear and specific informed consent language should be used to ensure that those who contribute biospecimens and/or data for research purposes comprehend any financial or nonfinancial benefits they may receive from the products, tests, or discoveries resulting from the research.
>
> **Recommendation 16.** As supplemental material to informed consent documents, a template or brochure should be developed that outlines how the NCI oversees research using biospecimens and clearly defines and communicates to research participants what they can expect in terms of research results. This brochure should define "benefit" and "sharing" and provide examples of nonfinancial benefits, such as aggregated research results, access to health care, products, and potential future treatments.

Recommendation 17. To demonstrate to the public that the fundamental goals of research are being met, a communication strategy for all research should be established that targets various populations such as minorities, slighted groups, and those with different lifestyles and habits. Such a strategy should include a regular reporting component, a brochure describing how the NCI oversees research, and a budget line item in research awards for technical writing and communication to fulfill these purposes.

3. *Providing Aggregate Research Results to Research Participants*

Providing aggregate research results enhances the public's understanding of the promise of research and builds trust. Exciting research results should be routinely presented using a newsletter or Web site. However, research participants need to understand that research outcomes result from long and complicated processes, and expectations of obtaining research results within a short timeframe are not reasonable. As part of the education process, research participants' expectations regarding benefits should be addressed. Individual benefits should not be sought; rather, research participation should be considered a benefit to society.

To address who should be responsible for providing research participants and contributors with access to products and benefits, distinctions should be made between the clinician-patient relationship and the investigator–research participant relationship. At times, clinicians may also serve as investigators, and it is in this role that they should address and provide products and benefits.

Recommendation 18. After research participants provide biospecimens, they should be able to stay informed as the research progresses. They should be able to learn the following:

- Whether samples have been shared with other researchers;
- Who is in charge of the sharing process and what are the confidentiality implications; and
- What general types of research studies have been performed using the biospecimens they provided.

B. Issues for Further Discussion

1. *Providing Individual Research Results to Research Participants*

Providing individual research results could benefit participants if the results have known clinical applicability—that is, they could affect a participant's health or his or her family's health now and in the future. Although consensus was not reached on this topic, it was suggested that the NCI seek to do the following:

- Develop national guidelines for clinical applicability. These guidelines should provide details on which results should be released to research participants.

- Detail the roles and responsibilities of the biospecimen resource, sponsor, principal investigator, and site where the research is performed.

- Require sites and their sponsors to establish a review board to review all research results conducted under their auspices. The board would determine whether the research results are of such clinical significance that participants should be notified. For highly significant clinical results, the review board would identify the research participants to be notified from their site.

- Develop policies covering the distribution of results, which also should provide the opportunity for participants to choose not to obtain research results.

- Establish auditing procedures to ensure adherence.

2. *Nature of Benefits*

Although discussants considered equitable and consistent access to benefits important, they felt it would be challenging to implement. For example, wide access to a new cancer vaccine may not be possible because of inequitable societal access to health care. In addition, discussants could not agree on the nature of benefits that should be provided to research participants and how these benefits would be provided. These discussions reflect ongoing, broader discussions in American society about access to health care.

VI. Next Steps/Conclusion

Workshop participants made significant progress in addressing biospecimen custodianship and ownership challenges, although some issues remain to be resolved. The NCI is committed to developing guidance on ethical and legal issues related to biospecimens that will promote cancer research while protecting the interests of research participants. The above discussions and recommendations regarding biospecimen custodianship will be carefully considered by the NCI, and the most critical issues will be expanded upon in scientific publications. Input obtained from a variety of stakeholders during the NCI Biospecimen Best Practices Forums also will be taken into account.[15] All contributions will be considered in future versions of the *NCI Best Practices* and in development of companion guidance documents. In addition, future iterations of the *NCI Best Practices* will be coordinated with other NIH initiatives, such as the Trans-NIH Bioethics Committee's Human Data and Specimen Subcommittee. Stakeholders will continuously be encouraged to visit the NCI OBBR Web site for updates on these issues[16] and to submit comments to the OBBR via e-mail at biospecimens@mail.nih.gov.

[15] Between June 2007 and January 2008 an educational outreach program was held across the United States to inform members of the intramural and extramural research communities about the *NCI Best Practices* and provide a forum for questions and feedback. For further information on these forums, visit http://biospecimens.cancer.gov/practices/forum/.

[16] http://biospecimens.cancer.gov/