SOUNDING BOARD

The Charitable Trust as a Model for Genomic Biobanks

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Advances in bioinformatics and genetics have made collections of biologic specimens and medical information valuable for pharmacogenomic research.[1] As a result, many large-scale data banks for genomics have emerged in the United States and abroad.[2] These large sets of tissue and blood samples and health data have profound medical, legal, ethical, and social implications for privacy, individual and group autonomy, and benefits to communities.[3-5] In the United States, a number of biotechnology companies are amassing samples — millions of them, in some cases — in private tissue banks.[6] Many of these companies act as brokers of tissue and of health data for a wide range of researchers.[6] Although this brokering has sparked ethical concerns,[2] the role of academic medical centers as suppliers for these private "biobanks" has received little attention.

When faced with financial constraints, some academic medical centers have chosen to transfer blood, tissue, and medical information directly to private biobanks in return for access for research and equity.[7,8] These and other novel collaborations may comply with federal rules, but they threaten to exacerbate problems in the existing system of federal oversight. Recent violations of the protection of human subjects at prestigious academic medical centers have brought institutional conflict of interest, the failure of institutional review boards (IRBs), and erosion of trust on the part of study participants into the spotlight, prompting calls for reform.[9-12] In order to protect rights and maximize scientific value, we suggest that biobanks be based on a new form of agreement among the medical institution, the researcher, and the donor community: one modeled on the charitable trust.

CONSENT FORMS AND PERMISSION

Informed consent has become the pillar of the protection of autonomy in research involving human subjects. It should be a process of communication, not simply a form to be filled out.[13] If individual subjects are being treated with respect, then they understand the purposes for which their tissue or blood will be used, comprehend the risks and benefits of particular projects, and retain the right to withdraw from the study at any time.[14]

Biobanks often ask research subjects for open-ended permission for future research projects.[3] Because it is impossible for the donor to make an informed choice about the risks and benefits of unspecified future research protocols, such permission should never be called informed consent.[4] Furthermore, open-ended permission makes it difficult for participants "to make informed and voluntary decisions throughout their involvement in the research,"[15] an emerging tenet of research ethics. As a result, Greely and others have argued persuasively that biobanks' requests for general permission should be allowed only if additional safeguards are in place.[3,4] These include review by the IRB of any subsequent research, clearly stated time limits for the project, an absolute right of withdrawal, disclosure of details about commercial arrangements, and provision of information about subsequent contact.[4]

Even with these safeguards, permission forms for private biobanks often frame the projects in misleading ways. First, the forms commonly give the impression that banked tissue and blood have no market value and would otherwise be thrown away. In fact, some tissue has been stored for years and has acquired market value.[16] Second, the characterization of projects in informed-consent forms as "hospital-based research protocols" is deceptive when hospitals broker tissue to private biobanks for commercial access. Third, the use of official hospital stationery and the collection of tissue by staff doctors and nurses give the misleading impression that the activity is a scientific and educational endeavor occurring in the context of medical care.

Full disclosure by private biobanks and hospitals would greatly improve the consent process for research subjects. However, that improvement alone would not solve other fundamental problems.

INSTITUTIONAL REVIEW BOARDS

IRBs at academic medical centers that approve protocols for obtaining informed consent and collecting and sending tissue and medical information to private biobanks introduce problems of accountability for participants and conflicts of interest for the institution.[17] In an increasingly common model for collaboration with the private sector, IRBs at hospitals not only have approved open-ended consent without time limits, but also have renounced ethical oversight of particular research projects. Examples of this structure can be found at the institutions that send tissue to Ardais Corporation, in Lexington, Massachusetts, which include Beth Israel Deaconess Medical Center, in Boston; Duke University Medical Center, in Durham, North Carolina; Maine Medical Center in Portland, Maine; and the University of Chicago.[8,18]

Federal regulations require that IRBs weigh the potential benefits of the knowledge to be gained from the research — for the participants or for society as a whole — against potential harm to the participants.[19] Even though a biobank may be unlikely to disclose a donor's genetic information, IRBs are not relieved of their duty to consider whether and how much future projects are expected to benefit the larger community. This delegation of authority by the IRBs conflicts with even the relatively lax opinions regarding acceptable open-ended consent in genomic research.[3]

Biobanks sometimes use "independent" IRBs to review research projects, but problems may arise. Although independent IRBs are geared to make quick decisions and can provide detached expertise, they may be under pressure to favor the interests of the institutions that hire them, arousing concern about IRB shopping.[20]

Furthermore, arrangements between medical centers and for-profit biobanks are often insufficient to keep donors apprised of new research uses for their samples. As a result, when patients agree to donate tissue or blood, they sign away their control and oversight. Patients might disagree with a particular commercial or scientific use of their material, but they have no right to be kept informed about it. A patient's right of withdrawal is worth little without a constant flow of new information.

PROPERTY RIGHTS AND BENEFITS TO THE COMMUNITY

The donation of body parts, tissues, and organs can have deep moral significance.[21] Should human tissue and medical data be barred from commercial exchange? What financial incentives are inappropriate for participation in research? These questions involve the competing values of fairness to donors, maintaining access to research materials, and incentives for innovation.[4,22,23] However, since human tissue, blood, and medical data are already being collected and sold, we also need to consider property rights and the benefits to the community.

The consent forms that private biobanks use often include clauses that waive donors' rights to their blood and tissue samples.[7,13,24] These clauses result from the increasing private investment in research and recent claims by tissue donors for a share of the profits derived from their samples.[16,23] These clauses are legally and ethically problematic. First, hospital consent forms that transfer property rights to institutional biobanks may be legally unenforceable as contractual promises owing to "power asymmetry" and "undue influence."[7] Second, the legal transfer of property might signal to the donors that they have given up any control of the samples,[25] which would undermine their right to withdrawal. Soliciting and obtaining gifts of tissue by informed consent overextends its traditional role and threatens the trust between the donor and the institution.

Consent forms that waive a donor's property rights are especially problematic in the case of biobanks that are privately held and under circumstances in which communities will realize little benefit. The National Research Council has stated that "in population studies, benefit to the population has become one of the critical issues in determining the ethical justification for the study itself, and sharing benefits with the population is critical in preventing exploitation."[26] This obligation holds not only for groups defined on the basis of ethnicity or disease but also for those defined on the basis of geographic region or health care institution. In fact, one reason that subjects donate samples to a biobank is for the greater good.

As a practical matter, biobanks would do well to consider this expectation of a collective benefit,

which has emerged forcefully in population-based biobanking projects and has even broken some of them apart. In Iceland, there was an acrimonious debate over what types of public benefits were owed in exchange for providing a biotechnology company with access to the nation's medical records.[7] Framingham Genomic Medicine, a company in Framingham, Massachusetts, that wanted to build a privately funded genome project with data from the Framingham Heart Study, proposed paying 5 percent of its profits to a charitable community-development fund in order to recognize the contribution of the community.[27] Nevertheless, the project foundered when the company was unable to reassure the National Institutes of Health and the community that it was offering the public a good enough deal.[27]

THE CHARITABLE-TRUST MODEL

Despite some debate about private-sector collaborations with medical institutions,[16,23] private biobanks are amassing millions of samples, and health centers seem ready to supply them. More creative thinking is needed to solve the problems in the governance of biobanks.

When a person agrees to donate tissue, the recipient has a responsibility to serve as a trustee, or steward, of the tissue in order to ensure protection of the contribution.[23,28] The National Research Council has suggested that for a worldwide collection of DNA, "a more sophisticated and complicated approach would be to form an international organization to serve as a trustee and fund-holder for all the sampled populations."[26] The charitable trust is a promising legal structure for handling such a set of obligations, for promoting donor participation in research governance, and for stimulating research that will benefit the public.[7,29]

Under a trust agreement, the tissue donor, or settlor, formally expresses a wish to transfer his or her property interest in the tissue to the trust. The permission form could be used for this purpose. The settlor appoints a trustee of the property, who has legal fiduciary duties to keep or use the property for the benefit of a specified party, the beneficiary.[30] In a charitable trust, the general public acts as the beneficiary.[30]

A charitable trust is an elegant and flexible legal model that has a number of advantages over private biobanks. First, charitable trusts accord well with the altruism that characterizes gifts of tissue.[21] If altruistic donations are solicited by hospitals for research, then the hospitals should act as stewards rather than as brokers. Second, the architect of the trust can provide the donor group with an advisory role in the governance of the trust.[30] We believe that the patient population of a medical center, with appropriate leadership from the institution, would have the necessary sense of community to make the advisory role meaningful. Finally, private biobanks may be forced to sell off their inventory in the event of bankruptcy, but charitable trusts have the advantage of longevity. This feature is important not only for donors but also for researchers who perform longitudinal studies.

STRUCTURING THE TRUST

Structuring a charitable trust requires careful thought about recruitment, permission, protection of donors' privacy and autonomy, and benefits to the community. To maximize its value, a biobank could contain tissue removed during surgery, as well as blood and serum collected from volunteers. Recruitment could take place in clinics and through outreach programs, but must be undertaken with caution. Surgical candidates for tissue donation should be recruited outside the context of clinical care, in order to avoid the misperception that care is contingent on consent. Mailings to community members and Web sites could be used to attract volunteers.

The permission form should contain the safeguards that Greely has proposed[4] — including review by the IRB of any subsequent research, absolute right of withdrawal, and full disclosure of commercial arrangements — which are unlikely to reduce the rate of participation substantially.[31] However, before patients or volunteers are presented with a permission form, they should be shown an explanatory videotape and have an opportunity to ask questions.[13]

In terms of safeguarding privacy, the trust would encrypt the identifying information on the tissue or blood sample before sending it to researchers, thus obviating the need for additional authorization by the donor under the new privacy regulations.[32] However, the trust would retain the key to the encryption, enabling it to update information.

Maintaining the biobank as a charitable trust governed by a board of trustees would allow the donor group to participate in the governance of the trust.[30] Forms of participation might include membership on the trust's IRB, membership on a do-

nor committee that has veto power over particular projects, and election of a donor to serve on the board of trustees. Research applications could be evaluated by the trustees according to a set of criteria that would ensure public benefit — by addressing public health failures, for example.

Donors would be asked to give permission for future research projects, but two features of the trust would safeguard their autonomy. First, the trust would keep donors informed about all research projects through a Web site and would specify a period of time during which donors could opt out of the research. This would encourage open-ended participation but would also allow donors to withdraw from a project. Second, the trust would require consultation with and consent by the community for studies that involve particular populations, such as members of an ethnic group. This would help protect group autonomy in genetic research.[33]

A cooperative model could have scientific advantages over private biobanks, whose customers are cut off from the donors. Since many common diseases in humans arise from a complex interaction between genes and the environment, the most useful biobanks for genomic research will contain information about a donor's phenotype, environmental exposures, and nutrition.[34] With a charitable trust, the ongoing acquisition of such data would be possible. If carefully constructed, the trust would allow donors to feel comfortable with the submission to the data bank of new medical data from their hospital visits and with being contacted if additional samples or specific information were needed. Donors could indicate on the initial permission form their willingness to be contacted.

FUNDING THE TRUSTS

A clear advantage of private biobanks is that they can quickly attract large amounts of venture capital. Raising the necessary funds for proper administration of a charitable trust would be a great but surmountable challenge.

Biobanks can attract the funding necessary to make them work with public benefit, not profit, as the organizing principle. For instance, the Marshfield Clinic, in Wisconsin, has developed what it calls the "personalized medicine research project," a nonprofit biobank that holds blood samples and medical information, as well as demographic and family information, from volunteers who are patients in the clinic's health network.[2] This biobank has received grants from Congress and the State of Wisconsin in support of its mission to construct a national resource. The National Health Service in the United Kingdom has also begun to develop a biobank, and there are nascent plans to start one on the national level in the United States.[2]

We believe that academic medical centers are qualified to take a leadership role in initiating and governing tissue trusts, for several reasons. First, academic medical centers have a unique relationship with tissue and blood donors and have access to medical and environmental data. Second, they have the means and experience to attract public grants and funding from private foundations. Third, they and the public would benefit from the development of good governance structures that would help educate and motivate potential donors. Also, such an endeavor accords well with the mission of teaching hospitals.

We are not rejecting market-based solutions for funding: indeed, biotechnology and pharmaceutical companies that want tissue or data from a hospital could be partners with the tissue bank in order to help fund it.[23] However, trustees that have been advised by donors should use funding models that seek research partnerships instead of tissue buyers. For instance, PXE International — a rare-disease group that has established a nonprofit blood and tissue bank — has generated funding by negotiating intellectual-property arrangements with commercial researchers.[35] The nonprofit model will facilitate research by maintaining open access and encouraging such partnerships.

CONCLUSIONS

As academic medical centers decide how to approach the difficult questions involved in the collection and storage of human tissue and blood, they should resist the temptation to assume the role of broker to private-sector biobanks. The charitable trust is an alternative that has clear ethical, legal, and scientific advantages. It can accommodate and foster the altruism, good governance, and benefit to the public that are necessary for the success of such a project over the long term. In addition, the tissue trust can comply with increasingly stringent rules about privacy and informed consent without losing its value as an information-rich genomic resource. Moreover, the channels for public participation and communication provided by a charitable trust would forestall the political battles that have stymied biobanking endeavors such as the Icelan-

dic Health Sector Database and the Framingham genome project. Based on the principle that genomic biobanking is both a scientific and a social endeavor, the charitable-trust model can foster a level of cooperation among teaching hospitals, researchers, and donor communities that will ensure responsible and fruitful use of research material.

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1. Rose H. The commodification of bioinformation: the Icelandic Health Sector Database. London: Wellcome Trust, 2001.
2. Kaiser J. Population databases boom, from Iceland to the U.S. Science 2002;298:1158-61.
3. Research involving human biological materials: ethical issues and policy guidance. Bethesda, Md.: National Bioethics Advisory Commission, 1999.
4. Greely HT. Breaking the stalemate: a prospective regulatory framework for unforeseen research uses of human tissue samples and health information. Wake Forest Law Rev 1999;34:737-66.
5. Annas GJ. Rules for research on human genetic variation — lessons from Iceland. N Engl J Med 2000;342:1830-3.
6. Eiseman E, Haga SB. Handbook of human tissue sources: a national resource of human tissue samples. Santa Monica, Calif.: RAND, 1999.
7. Winickoff DE. Governing population genomics: law, bioethics, and biopolitics in three case studies. Jurimetrics 2003;43:187-228.
8. Connolly A. Ardais ambitious with plans for clinical genomics. Boston Business Journal. November 22, 2002.
9. Institutional review boards: a time for reform. Washington, D.C.: Office of Inspector General, June 1998.
10. Shalala D. Protecting research subjects: what must be done. N Engl J Med 2000;343:808-10.
11. Barnes M, Florencio PS. Financial conflicts of interest in human subjects research: the problem of institutional conflicts. J Law Med Ethics 2002;30:390-402.
12. Steinbrook R. Improving protection for research subjects. N Engl J Med 2002;346:1425-30. [Erratum, N Engl J Med 2002;346:1838.]
13. Annas G. Reforming informed consent to genetics research. JAMA 2001;286:2326-8.
14. Faden RR, Beauchamp TL. History and theory of informed consent. New York: Oxford University Press, 1986:151-232.
15. Ethical and policy issues in research involving human participants. Bethesda, Md.: National Bioethics Advisory Commission, August 2001:xvii.
16. Kolata G. Sharing of profits is debated as the value of tissue rises. New York Times. May 15, 2000:A1.
17. Rothstein MA. The role of IRBs in research involving commercial biobanks. J Law Med Ethics 2002;30:105-8.
18. Ardais Web site. (Accessed August 28, 2003, at http://www.ardais.com/national_initiative/index.html.)
19. 45 C.F.R. § 46.111(a)(2).
20. Institutional review boards: the emergence of independent boards. Washington, D.C.: Office of Inspector General, June 1998. (OEI-01-97-00192.) (Also available at http://www.researchroundtable.com/pdfiles/irbemergence.pdf.)
21. Nelkin D, Andrews L. Homo economicus: the commercialization of body tissue in the age of biotechnology. Hastings Cent Rep 1998;28(5):30-9.
22. Harrison CH. Neither Moore nor the market: alternative models for compensating contributors of human tissue. Am J Law Med 2002;28:77-105.
23. Ashburn TT, Wilson SK, Eisenstein BI. Human tissue research in the genomic era of medicine: balancing individual and societal interests. Arch Intern Med 2000;160:3377-84.
24. Beskow LM, Burke W, Merz JF, et al. Informed consent for population-based research involving genetics. JAMA 2001;286:2315-21.
25. Singer JW. Entitlement: the paradoxes of property. New Haven, Conn.: Yale University Press, 2000:29-30, 83.
26. National Research Council, Committee on Genome Diversity. Evaluating human genetic diversity. Washington, D.C.: National Academy Press, 1997.
27. Rosenberg R. Questions still linger on heart study access. Boston Globe. February 21, 2001:D4.
28. Jeffers BR. Human biological materials in research: ethical issues and the role of stewardship in minimizing research risks. ANS Adv Nurs Sci 2001;24(2):32-46.
29. Gottlieb K. Human biological samples and the laws of property: the trust as a model for biological repositories. In: Weir RF, ed. Stored tissue samples: ethical, legal, and public policy implications. Iowa City: University of Iowa Press, 1998.
30. Bogert GG, Bogert GT. The law of trusts and trustees. 2nd ed. St. Paul, Minn.: West Publishing, 1992:323-9.
31. Malone T, Catalano PJ, O'Dwyer PJ, Giantonio B. High rate of consent to bank biologic samples for future research: the Eastern Cooperative Oncology Group experience. J Natl Cancer Inst 2002;94:769-71.
32. HIPAA Privacy Rule, 45 C.F.R. § 164.501-508.
33. Greely HT. The control of genetic research: involving the "groups between." Houston Law Rev 1997;33:1397-430.
34. Olden K, Wilson S. Environmental health and genomics: visions and implications. Nat Rev Genet 2000;1:149-53. (Also available at http://www.niehs.nih.gov/ododd/articles/visions_and_implications.pdf.)
35. Smaglik P. Tissue donors use their influence in deal over gene patent terms. Nature 2000;407:821.