HEALTH LAW, ETHICS, AND HUMAN RIGHTS

# Rules for Donations to Tissue Banks — What Next?

Leonard Glantz, J.D., Patricia Roche, J.D., and George J. Annas, J.D., M.P.H.

Michael Crichton's *Next*[1] is a fictional creation of multiple catastrophes emanating from the real-life case of John Moore, in which the California Supreme Court ruled in 1990 that Moore did not own his cells after they were removed from his body.[2] As human tissue has become commercially useful, and as tissue banks storing and providing samples for research have flourished, the question of who owns the tissue has become more vital. *Next* got mixed reviews, but even many scientists, such as Michael Goldman, who reviewed the book in *Nature*, agree with Crichton that it is imperative that we "establish clear guidelines for the use of human tissue" in medical research.[3] Legal opinions from Florida[4] and, most recently, Missouri[5] supplement the Moore case and together provide a foundation on which to build these guidelines.

## THE CASE OF JOHN MOORE

In 1976, John Moore was treated for hairy cell leukemia by hematologist–oncologist David W. Golde at the University of California at Los Angeles (UCLA). As is standard procedure for the treatment of this disease, Golde recommended the removal of Moore's spleen, which had enlarged from about 1/2 lb (0.2 kg) to more than 14 lb (6.4 kg). Moore improved quickly after the surgery. Golde took a sample from the spleen and isolated and cultured an immortal cell line capable of producing a variety of valuable products, including the lymphokine granulocyte–macrophage colony-stimulating factor. In 1983, UCLA applied for and was granted a patent on the cell line. Moore had been returning to California to see Golde about every 6 months. He told an interviewer that he never would have known about the existence of the cell line had Golde not called him in September 1983 and told him he had "missigned the consent form" (circling I "do not" grant instead of I "do" grant UCLA all rights in "any cell line"). Moore consulted an attorney and filed suit against UCLA and Golde in 1984.[6]

### MOORE IN THE COURT OF APPEALS

The trial court decided that Moore had no rights to his cells. Moore brought his case to a California Court of Appeals, which in 1988 reversed the trial court's decision.[7] Judge David Rothman, writing for the 2-to-1 majority, focused on just one issue: If Moore could prove the facts he alleged regarding "conversion" — or theft — of his cells, would he win the lawsuit under California law? Conversion involves a civil lawsuit that essentially claims that a defendant wrongfully took or retains the plaintiff's property. The plaintiff must prove ownership or right to possession of the property at the time of the conversion, wrongful conversion or disposal of the property, and damages.

According to California statute, "The ownership of a thing [property] is the right of one or more persons to possess and use it to the exclusion of others." Although we are unaccustomed to thinking of the human body as property, the court noted that "the essence of property interest — and the ultimate right of control . . . exists with regard to one's own body." This finding negated the defendants' position that everyone but the source of the cells could own them. Similarly, the defendants' contention that a diseased spleen that has been removed from a patient is a thing of no value was negated by the fact that the cells from the spleen formed the foundation of a multimillion-dollar industry.

The defendants next argued that the removed spleen was "medical waste" that Moore abandoned for the physicians to dispose of as they saw fit; consequently, there was no conversion or wrongful disposal. Rothman found that if the spleen had been disposed of by "internment or incineration," in accordance with the usual practice, Moore could not complain. But the judge

concluded, "Any use . . . not within the accepted understanding of the patient is a conversion" because it cannot be presumed "that the patient is indifferent to" other uses, such as commercial exploitation.[7] The dissenting judge would have dismissed the case because he found Moore's claim trivial, and the tissue to be "like unformed clay or stone transformed by the hands of a master sculptor into a valuable work of art."[7] The dissenting judge also thought that allowing patients to sell or otherwise profit from their organs and tissues would impede medical progress.[7]

Since Moore was not claiming that his spleen itself was valuable but rather that Golde had used it to make a product of value, and since there was no precedent directly on this point, the appeals court opinion offers novel arguments on the question of who owns the result when raw materials are converted into a valuable product. For example, under ancient Roman law, when agricultural crops were in the ground, they were owned by the landowner, but picked fruits and vegetables were owned by the farmer who worked the land. Trees taken from the land, however, belonged to the landowner. Is a removed spleen more like an ear of corn or an oak tree? Is Moore like a landowner (who owns his body) and the doctor like a farmer (who plucks fruit)? Rothman made another analogy to refute the conclusion that a diseased spleen is worthless. He noted that even though a landowning farmer might pay an oil company to remove oil that is ruining the corn crop, the farmer is still entitled to a share of the refinery's profits from the product of the land.[7] Likewise, even if the physician–researcher owns the created cell line, he may still owe the patient something.

Since the cells in human tissue are living and reproduce, perhaps they are more analogous to farm animals than to fruits or vegetables. The progeny of animals are the property of the mother's owner. Is the cell line equivalent to Moore's "progeny"? Similarly, an owner wrongfully deprived of livestock is owed the value of the eggs from converted chickens and milk from converted cows.[6] Are Moore's immortal cells like chickens, and the protein products derived from them like eggs? The need to resort to cases that involve the ownership of corn, trees, cows, and eggs demonstrates the need to create modern rules that deal directly with the ownership and use of human tissue.

### MOORE IN THE CALIFORNIA SUPREME COURT

The California Supreme Court ignored all of these potentially useful, if somewhat amusing, property analogies. It simply decided that Moore's physician should have disclosed his financial interest in using his patient's spleen for research and commerce but that Moore had no property interest in his cells after they had been removed from his body.[2]

The court's reasoning was straightforward but unsophisticated. The court noted, for example, that California statutes that govern the disposition of excised tissue do not give property rights to patients but failed to note that these statutes deal only with tissue removed from corpses. The court also argued that the patented cell line was "both factually and legally distinct from the cells taken from Moore's body."[2] This is true, but as the appeals court noted, it does not mean that Moore has no interest in the fruits of the discoveries that required the use of his unique cells.

The underlying reason for the California Supreme Court's ruling against Moore on the issue of property can be found in its statement of public policy: "The extension of conversion law into this area will hinder research by restricting access to the necessary raw materials [and] destroy the economic incentive to conduct important medical research."[2]

## GREENBERG V. MIAMI CHILDREN'S

The next major case was from Florida.[4] The plaintiffs were families affected by Canavan disease, a spongiform degeneration of the central nervous system. They had persuaded Dr. Reuben Matalon to try to identify the gene responsible for the disease and were active creators and supporters of the research, not merely tissue providers. They created and maintained the Canavan Registry, a repository for their tissue samples and medical information, and engaged Matalon with the goal of developing an affordable and widely accessible genetic test for Canavan disease. Matalon successfully identified the gene and subsequently developed prenatal and carrier tests for the disease.

Without the plaintiffs' knowledge, Matalon obtained a patent for the relevant genetic sequence, thereby securing the rights of his employer, Miami Children's Hospital Research Institute, to control genetic testing for Canavan disease in clinical care as well as research. Miami Children's exercised its patent rights in a way that the plaintiffs believed defeated the purpose for which they had joined forces with Matalon in the first place. They had not provided resources (tissue samples, information, and funds) with the understanding that these resources would be used for the economic benefit of Matalon or his institution but had done so to develop an affordable diagnostic test. The plaintiffs had six specific claims, and the trial judge dismissed five of them.[4]

One claim was similar to one made in *Moore* — the wrongful conversion of the plaintiffs' property, with the property being the samples (and the information derived from them) held in the Canavan Registry. The judge noted that under Florida law, conversion "is an unauthorized act which deprives another of his property permanently or for an indefinite time." Application of this law involves two inquiries: whether property was involved, and if so, whether the requisite deprivation or misuse of that property occurred. The trial judge declined "to find a property interest in body tissue and genetic information voluntarily given to defendants."[4] This conclusion was based primarily on the fact that under Florida law "the property right in blood and tissue samples . . . evaporates once the sample is voluntarily given to a third party."[4]

Nevertheless, the judge went on to consider whether the tissue samples were used for a purpose unintended by the plaintiffs. He found that the tissue samples were used only for medical research (as intended by the plaintiffs) and so concluded that there could be no liability for conversion. In rejecting the plaintiffs' claim that they had not provided samples to be used for commercial purposes, he drew a distinction between commercialization of the material in the Canavan Registry and commercialization of the fruits of the research conducted by using the material in the registry. In this case, the fruits were identified as the patented material (the genetic sequence).

Similar to the ruling by the California Supreme Court in *Moore*, the Florida ruling reflected the judge's concern that a finding for the plaintiffs would "cripple medical research."[4] This ruling, then, was as pragmatic and result-driven as that in *Moore*, but it does add another element: in *Moore*, the property at issue comprised the tissue and the cells that were produced from it; in *Greenberg*, the property questions involved the tissue and access to a diagnostic test developed using the tissue. In both cases, patents were used to make the products derived from the tissue more valuable.

## THE CASE OF WILLIAM CATALONA

The Missouri dispute began when Dr. William Catalona, a prominent researcher on prostate cancer, decided to leave Washington University in St. Louis for Northwestern University in Chicago and to take "his" tissue samples with him.[5] These samples were collected from patients who had signed research consent forms that authorized the storage and use of their tissue for future research. Before leaving, Catalona sent 10,000 letters to his former patients asking them to sign and return an enclosed form that read as follows:

> I have donated a tissue and/or blood sample for Dr. William J. Catalona's research studies. Please release all samples to Dr. Catalona at Northwestern University upon his request. I have entrusted these samples to Dr. Catalona to be used only at his direction and with his express consent for research projects.[5]

Six thousand patients returned completed forms. Washington University filed suit against Catalona, asking the court to declare that the university was the exclusive owner of the tissue repository and the samples in it.

According to the reasoning in *Moore* and *Matalon*, people own their tissues when the tissues are part of their bodies, but ownership becomes less clear once it is separated from the body. Nonetheless, the tissues still must be controlled by someone, whether for proper disposal or other use. And the way law thinks about control of objects is through property law, especially when there is a transfer from one entity to another. The transfer of property usually takes one of two

forms — a sale or a gift. Since the tissues were not sold in *Catalona*, the question was whether a gift was made, and if so, to whom.

Catalona's form letter indicates that he believed the tissue was "donated" to him — that he was the recipient of a gift. But if this were so, he would have no reason to write the letter to the donors in the first place. If the tissue was a gift to Catalona, he could have asked the university directly to transfer "his" blood and tissue samples. If a grateful patient had given Catalona a first-edition medical text, when Catalona moved to a new university he would not have asked that patient to write to the university asking it to transfer the book to him. He would simply have taken it with him. Alternatively, if the patient had given the book to the university library, even in Catalona's name, he could not take it without the university's permission.

A gift consists of three elements: First, the donor must have the present intent to make a gift. Second, the property must be transferred from the donor to the recipient. Finally, the recipient must accept the gift, at which moment it belongs to the recipient. Once a gift is made, the donor has no further property interest. It is, nonetheless, possible to make a conditional gift. For example, a person could create an endowment for a university to conduct cancer research, but no other type of research, with a stipulation that the money be returned if it is ever used for another purpose. A person can also condition a gift on the occurrence of an event. A case cited by the appeals court involved the ownership of an engagement ring given in contemplation of marriage when the wedding was called off. The court ruled that the ring was to become a gift at the time of the wedding. Because the groom cancelled the wedding, and the bride was prepared to marry and meet the condition of the gift, the court decided that the ring was hers.[5,8]

The appeals court agreed with the trial court that an unconditional gift of tissue was made to Washington University, not to Catalona. The court based this conclusion on its findings that the consent forms signed by the patients were Washington University forms, the patients were directed to university personnel for answers to questions, the university controlled and paid for the repository, and the university controlled the use of the samples. Moreover, Catalona was at all times employed by the university and worked on its behalf, and there was no indication that any patient had made a direct gift to him.[5,9]

## THE CONFUSION

The conflicts that ultimately brought these cases to court were the result of confusion over who had ultimate control of the tissue samples from which various products were derived. The confusion was shared by the physicians who collected the samples, the institutions that stored the samples, the people who provided the samples, and the corporations that patented the products. Analysis of the court opinions also demonstrates a profound lack of clarity in the minds of the judges as to what types of law should be used to resolve the novel legal questions presented. Since there are virtually no judicial precedents, the courts have had to resort to analogies that have proven difficult to apply and have sometimes created more confusion than clarity in the law.

An example of role confusion is found in the form, titled "Medical Consent and Authorization," that Catalona sent to his patients. Despite its title, this document is not a medical consent form; it is simply a request to transfer property. This is a mischaracterization, but how should we characterize people who provide their tissue for banking? Throughout the *Catalona* opinion, they are referred to as research participants.[5] Both parties to the lawsuit and the courts apparently viewed research participants and tissue providers as identical. But this is a serious conceptual error that adds more problems to the matter of tissue collection, storage, and use than it purports to solve.

Research subjects have substantial rights. In addition to consenting at the outset, they have the right to discontinue playing the role of research subject at any time.[10] They never make an irrevocable "gift" of themselves. A person can be in a clinical trial and not provide tissue. But a person can also provide tissue and not be a research subject. When these two distinct roles are confused, problems are created. The distinct roles are easier to see when other types of property are involved. For example, a subject in a clinical trial may give the researcher a computer and thus be a both a research subject and a donor. As a research subject, she can, under

the law, terminate her participation in the research, but she is not entitled to get the computer back because it was a gift over which she has lost control. Tissue donors are no more research subjects than computer donors are.

This role confusion also exists in the minds of federal regulators. Current guidance from the Office for Human Research Protections states: "Under the definition of human subject at 45 CFR 46.102(f), obtaining identifiable private information or identifiable specimens for research purposes constitutes human subjects research. Obtaining means receiving or accessing identifiable private information or identifiable specimens for research purposes."[11]

As the Catalona court points out, the guidance issued by this office — as opposed to regulation — is not law and is not binding. The Office for Human Research Protections argues that the mere obtaining of "identifiable specimens" for "research purposes" is itself research. According to this definition, it is possible for there to be a research subject in the complete absence of any research. The collection of money, equipment, personnel — or tissue samples — in the contemplation of research, which may or may not ever be conducted, is not research. The Office for Human Research Protections thus makes the same conceptual error the courts make. A piece of tissue, identifiable or not, constitutes neither research nor a research subject. At some point it may be used for research, at which time identifiable information might be derived about the donor, and it is the use of the tissue for research that requires human subject protection.

The classification of tissue providers as research subjects also raises the difficult and unresolved problem of terminating participation — if tissue providers are the same as research subjects, they should be able to discontinue their participation at any time. But what does this mean? Catalona argued this meant that tissue providers continue to have control over samples and can have the samples returned to them or transferred to someone else, such as Catalona. Washington University argued that discontinuance meant that the university could destroy the samples, continue to store them without using them, or remove all identifiers from them. But if Washington University had been the recipient of an unconditional gift, as it argued, the tissue provider could not require any of these actions. It is as if the generous donor who made a gift of the first-edition textbook could at any time require the library to destroy the book or remove it from use. This makes no sense as a matter of law.

The Catalona case nonetheless helps clarify the legal status of human tissue. It is property. It starts out as the property of the person from whom it is taken, it can be given by the person to an institution or to another person, and the nature of the gift is determined by the intent of the giver. Traditional standards of property law apply to human tissue removed from a living person.[5] On the other hand, by confusing tissue providers with human subjects — and gift law with human subject regulations — the case also adds to the current confusion.[12]

## RESOLVING THE CONFUSION

Resolving the confusion requires a recognition that the rules of protection for human subjects cannot reasonably be applied to tissue donation. Collecting and storing human tissue is not research, nor is it new, experimental, or even controversial. Human tissue is treated as property under the law, but the continuing controversies about the appropriate use of human tissue, including its use as a commercial product, suggest that human-tissue donation needs its own rules and standards. Agreement on such standards has eluded tissue collectors to date, but *Catalona* may provide the catalyst to move us to the next phase: regulating tissue donation and banking by creating, by means of statute or best practices, a formalized process for tissue donation. Analogies to crops, livestock, oil, and even books and computers are simply inadequate.

A formalized process for human-tissue donation should require explicit recognition that a gift is being made, should identify the recipient of the gift, and should specify whether the gift is conditional or unconditional. If a conditional gift is intended, the donor must specify the conditions, including any requirement that the tissue be destroyed if those conditions are not met. The statutory approach would be to draft a law similar to the Uniform Anatomical Gift Act, which governs the donation of dead bodies and tissue removed from corpses. Such a law would (or at least should) also determine under what

circumstances, if any, people would be permitted to sell their tissue and what buyers could do with it. Current federal law, for example, prohibits the purchase or sale of human organs for transplantation, and current national voluntary guidelines prohibit the purchase and sale of human ova, at least for stem-cell research.[13,14]

Clear rules for collecting and storing human tissue would benefit both collectors and providers.[15] On the other hand, it is worth emphasizing that these rules will not resolve the question of what can be done with the stored tissues — in either existing or future collections. The reason is that before it was possible to analyze DNA, the primary legal issue was the property issue addressed in *Moore:* Who owned the tissue and its products? With the advent of DNA analysis, the property question has been joined with a privacy question: What can be done with the personal, private information encoded in human tissue? This issue is starkly presented, for example, by the "consent and legal agreement" form used by 23andMe, one of the new Web-based personal genetics companies. The form states that "after analysis, your remaining DNA and saliva samples will be destroyed." The agreement also states, however, that the information derived from the DNA can be used by the company and its partners "as part of our scientific research with the purpose of advancing the field of genetics." We have previously suggested a comprehensive law protecting genetic privacy to address this concern.[16,17] Of course, if the stored tissue samples cannot be linked to individual donors, the privacy issue disappears and property concepts can be used exclusively to establish tissue-bank practices.

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From the Department of Health Law, Bioethics, and Human Rights, Boston University School of Public Health, Boston.

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